Original article

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Effect of levetiracetam on cognitive functions and quality of life: a one-year follow-up study

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ABSTRACT – *Purpose.* The purpose of the study was to assess changes in cognitive functions and quality of life in patients with epilepsy over one year of treatment with levetiracetam (LEV) as add-on therapy. *Methods.* Thirty-two patients (16 women; 16 men) who received LEV as an add-on treatment were included, and 27 completed the one-year follow-up period. Extensive neuropsychological assessments, together with a quality-of-life questionnaire were administered at baseline and at one, three, six and twelve months after beginning the add-on treatment. Patients received LEV starting with 500 mg/day in the first week, increasing by a further 500 mg/day per week until a target dose of 2 000 mg/day was reached by the end of the first month. *Results.* At the one-year follow-up, a significant improvement was observed in measurements of prospective memory, working memory, motor functions, verbal fluency, attention and quality of life. Performance for neuropsychological and quality-of-life tests was not affected by external variables such as seizure reduction or changes in previous anti-epileptic treatment. Slight changes between patients were observed, but these were not clinically significant.The limited sample size and the lack of a control group should be mentioned as limitations of the study. No control group was evaluated as in our clinical practice it was difficult to establish a comparable group of patients. Changes in the different variables were assessed by comparing baseline information with follow-up results.Despite the study limitations, we consider that the one-year treatment period provides valuable information regarding the drug's long-term effects in this setting. *Conclusions.* Results of the present study suggest that long-term LEV treatment as add-on therapy does not interfere with cognitive function and improves quality of life.

Key words: cognitive functions, quality of life, epilepsy, levetiracetam

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Patients with epilepsy generally have more behavioral and cognitive deficits than the general population. Biological factors such as type of seizure, underlying pathology, age-at-onset, and also psychosocial factors and therapeutic interventions, may influence these deficits (Lee and Chan 2002, Motamedi and Meador 2003). Anti-epileptic drugs (AED) are one of the most common therapeutic approaches, and these may impair cognitive

function (Meador *et al.* 1999, Motamedi and Meador 2003). However, it has been observed that once epileptic seizures are controlled, affected functions and behavior may improve (Malagón-Valdéz 2003).

In recent years, a new anti-epileptic drug, levetiracetam (LEV), has been introduced to treat partial complex seizures with or without secondary generalization (Mitchell and Sander 2001, Herranz and Argumosa 2002). It has a favorable pharmacokinetic profile, with rapid, almost complete oral absorption (Mitchell and Sander 2001), rapid titration and a low toxicity profile (Arroyo 2002). It is safe (Salas-Puig *et al.* 2004), well tolerated by patients (French *et al.* 2001) and effective in the treatment of refractory epilepsy (Shorvon *et al.* 2000, Ben-Menachem and Falter 2000, Cereghino *et al.* 2000, Betts *et al.* 2000, Krakow *et al.* 2001, Salas-Puig *et al.* 2004).

Studies on the effects of LEV on cognitive functions in normal and amygdala-kindled rats (Lamberty and Klitgaard 1998, Lamberty *et al.* 2000), and in healthy volunteers (Mecarelli *et al.* 2004), have reported no negative consequences. In patients with epilepsy, long-term follow-up data concerning cognitive performance after LEV treatment are lacking; one study involving a small sample of patients showed no significant short-term changes (Neyens *et al.* 1995); another controlled study found that patients improved in tasks of verbal fluency and attention when compared with the pretreatment results (Piazzini *et al.* 2006).

In addition to cognitive performance, an important aspect related to patients with epilepsy is health-related quality of life (QoL) (Johnson *et al.* 2004, Szaflaraski and Szaflarski 2004). In the few studies that have evaluated QoL after LEV treatment, improvements have been reported with respect to several measures (Cramer *et al.* 2000), and these were maintained even at the four year follow-up (Cramer and Van Hammee 2003).

As there are insufficient data concerning cognitive status and QoL after LEV treatment, we conducted a long-term study to evaluate these two sets of variables in a sample of patients with refractory epilepsy. Efficacy of treatment was also assessed.

Patients and methods

Patients

Thirty-two patients with refractory epilepsy were prospectively recruited from a sample of outpatients, regularly attending the epilepsy unit at a tertiary care hospital (Hospital de la Santa Creu i Sant Pau) in Barcelona, Spain.

There is, as yet, no single definition of refractory epilepsy (Berg and Kelly 2006, French 2006, Berg 2006), and the criteria we used for inclusion were: previous failure to more than three anti-epileptic treatments and the occurrence of seizures in the previous three months.

All patients were aged 18 or over and receiving treatment with stable doses of ≤ two anti-epileptic drugs in at least the four weeks prior to baseline assessment.

Owing to the nature of the study, we excluded patients with neurological or progressive systemic condition that could affect their quality of life or their performance in neuropsychological tests. Patients with mental retardation, defined as an intellectual quotient ≤ 75, were not eligible.

Design

Following inclusion in the study, a complete neuropsychological assessment was performed before treatment with LEV was started in order to obtain baseline measures. The same neuropsychological assessment was repeated at one, three, six and twelve months after the treatment had begun.

To control external variables, the neuropsychological evaluation was always performed under the same conditions. Parallel forms of the tests were used throughout the study. QoL was assessed, and seizure diaries were kept by the patients and reviewed by the epileptologist at each visit.

The initial dose of LEV was 500 mg/day during the first week, increasing by 500 mg/week until a dose level of 2 000 mg/day was reached by the fourth week. This final dose was maintained throughout the study period. Because of drug intolerance, one patient continued to receive only 1 000 mg/day. In two patients, the daily dose was increased to 3 000 mg/day for the last six months of the follow-up period.

To study the effectiveness of LEV as adjunctive therapy in this group of patients, we recorded the number and type of seizures in the three months prior to the study. This information was collected retrospectively from each patient's seizure diary. Seizures were classified as simple, complex or secondary generalized according to the International League Against Epilepsy (ILAE) (1989).

To assess cognitive function, we used tests that have been shown to be effective in detecting cognitive changes in patients with similar characteristics (Leach *et al.* 1997, Meador *et al.* 1999, Dodrill *et al.* 1999). A quality-of-life scale for epilepsy, translated and validated in Spanish, was also used (Torres *et al.* 1999).

Informed consent to be included in the study was obtained from all patients.

Neuropsychological assessment

Patients underwent a comprehensive neuropsychological test battery that included measurements of attention, memory, motor and frontal functions.

An adapted version of the Continuous Performance Test (CPT) (García-Sánchez and Estévez-González 1991) was used to assess sustained attention.

The Spanish version of the Rivermead Behavioral Test (Wilson *et al.* 1991), translated by Mozaz M. in 1991, was used for prospective memory. The Rey Auditory Verbal Learning Test (Lezak 1995) was administered for verbal memory; the letters and numbers subtest of the WAIS Intelligence Scale (Wechsler 2001) for working memory, and Form F of the Benton Visual Retention Test (Dodrill *et al.* 1999) for visual memory.
To assess motor functions - motor speed and manual dexterity - we used the Purdue Pegboard Test (Spreen and Strauss 1998).
For frontal functions, we used the Word Fluency Test (Benton and Hamsher 1983) for language fluency; the Trail-Making Test (Form B) (Lezak 1995) for visual attention and motor speed, and the computerized version of the Stroop Test adapted by Estévez-González (1991) for resistance to interference and flexibility.

Quality of life

The Quality of Life (QoL) in Epilepsy Inventory - QOLIE 31 (Torres *et al.* 1999), includes 31 items divided into seven subscales that assess seizure worry, overall QoL, emotional well-being, energy/fatigue, cognitive functioning, medication effects and social functioning. The total score is obtained from a weighted average of the subscales.

Statistical analysis

Results were analyzed with the Statistical Package for the Social Sciences for Windows (SPSS 14.0). Analysis of variance, ANOVA, for repeated measures was used to determine any significant changes in the neuropsychological assessment and quality of life during the study period. The non-parametric Friedman test was used to compare changes in the number of seizures during the treatment period. A two-way ANOVA was performed to assess whether cognitive variables and QoL were influenced by a decrease or discontinuation in previous treatment and to identify an association between seizure control and neuropsychological performance.
In view of the study objectives, no adjustments for multiple comparisons were made.

Results

Patient data

Of the 32 patients included in the study, 27 (13 women and 14 men) completed the one-year follow-up. Five patients withdrew from the study: one had adverse effects (nausea), and treatment showed a lack of efficacy, one refused to continue the neuropsychological follow-up, a third was diagnosed with ovarian cancer during the study period and started chemotherapy, another discontinued treatment during the second month of follow-up because she had not observed any significant changes in seizure frequency, and one decided to continue the treatment in a different hospital. The dropout rate was therefore 15.6%.
The mean age was 39.18 (SD 11.6) years. Educational level was determined by the number of years of education: five participants had between four and six years of education, 15 between seven and 12, and seven more than 12 years. These findings are comparable with the normal population in Spain where figures for educational attainment are below the OECD average for all ages (OECD 2007). Nine patients were unemployed, five because of epilepsy. The mean duration of the disease was 23.77 (SD 14.9) years, and the etiology of epilepsy varied among patients.

Concomitant treatments and adverse effects

Patients were on treatment with different anti-epileptic drugs, to which LEV was added. There were 16 patients on monotherapy, carbamazepine was used in bitherapy in eight patients and the remaining patients (three) were taking combinations of two treatments. *Table 1* shows the group data.
Due to the improvement in seizure control, previous anti-epileptic treatment was changed. After three months of treatment, concomitant medication was modified in six patients, and after six months it was modified in eight patients. Concomitant treatment was changed in one of these patients because of adverse effects. Only in one patient was the concomitant treatment changed after the first month of follow-up. From the group of patients who were undergoing treatment with one AED before LEV was added, three changed to LEV monotherapy and five reduced the daily dose of the previous treatment. Of the patients who had previously been treated with two AED, four patients discontinued one of the AED and four reduced the daily dose of one of the treatments. The remaining patients continued with the same treatment as previously. In two patients, the LEV dose was increased to 3 000 mg/day six months after starting the treatment. Only one patient continued to take only 1 000 mg/day of LEV because of lack of tolerability. *Table 2* shows the changes made to concomitant medication.
While taking LEV, some patients reported adverse effects such as somnolence (five patients), irritability and aggressiveness (one patient), fatigue and tiredness (one patient) and insomnia (one patient). These adverse effects improved within the first three months of treatment.

Seizure frequency

We compared the numbers of seizures at baseline, three, six and twelve months following the start of treatment. Throughout the study period, there were no significant changes in simple seizures ($p = 0.523$); complex seizures showed a significant improvement ($p < 0.001$); there was a trend to significance for secondary generalized seizures ($p = 0.088$) and there was a significant improvement in generalized seizures ($p = 0.002$): see *table 3* for the mean

Table 1. Patients data.

Patient	Gender	Age	Years of disease	Etiology	Treatment	Working status	Years of education	Seizure type
1	F	50	11	Unknown	VPA	No	7-12	CP
2	F	44	43	Unknown	CBZ	No	7-12	CP
3	M	59	43	Unknown	VPA	Yes	7-12	SP
4	M	36	9	Cranial trauma	VPA	Yes	7-12	SP/PSG
5	M	48	10	Cerebrovascular accident	LTG	Yes	4-6	SP
6	F	40	23	Cerebral neoplasia	CBZ, CLB	Yes	7-12	SP/CP
7	F	43	29	Other	CBZ, TGB	Yes	+ 12	SP/CP
8	M	42	40	Other	TPM	Yes	7-12	SP
9	F	27	11	Unknown	TPM	Yes	7-12	SP/PSG
10	M	29	16	Unknown	CBZ, VPA	Yes	+ 12	G
11	F	20	19	Cerebral infection	CBZ	No	7-12	CP
12	M	24	9	Unknown	CBZ	Yes	+ 12	G
13	F	49	46	Unknown	PHT	Yes	+ 12	CP
14	M	45	29	Perinatal event	CBZ, PHT	Yes	4-6	CP
15	F	36	21	Cerebral infection	CBZ, GBP	Yes	7-12	SP/CP
16	M	44	31	Cerebral infection	CBZ	No	7-12	SP/CP
17	M	42	41	Perinatal event	CBZ, LTG	No	7-12	SP/CP/PSG
18	F	40	29	Unknown	TPM, CLB	No	7-12	SP/CP/PSG
19	F	72	63	Cerebral infection	LTG	No	4-6	CP/PSG
20	F	37	35	Perinatal event	CBZ	Yes	7-12	CP
21	F	38	31	Unknown	VPA, LTG	Yes	+ 12	G
22	M	24	19	Other	VPA, TGB	Yes	+ 12	PSG
23	M	29	9	Perinatal event	CBZ	Yes	+ 12	CP
24	M	35	2	Other	VPA	Yes	7-12	SP/CP
25	F	49	39	Unknown	TPM, CBZ	No	4-6	PSG
26	M	20	12	Other	CBZ, TGB	Yes	7-12	CP
27	M	59	16	Unknown	CBZ	No	4-6	CP

M: male; F: female; CP: complex partial seizures; SP: simple partial seizures; PSG: partial seizures evolving to secondarily generalized seizures; G: generalized seizures; VPA: valproate; CBZ: carbamazepine; LTG: lamotrigine; CLB: clobazam; TGB: tiagabine; TPM: topiramate; PHT: phenytoin; GBP: gabapentin.

range of seizures and significance. At the end of the study period, 11 of the 27 patients were seizure-free and two had a decrease of over 50% in the number of seizures for at least six months.

Even though all patients were included in all analyses, p values varied greatly. We consider this was mainly due to the wide variability in the number of seizures within the group.

Effects of LEV on cognitive functions and QoL

Regarding cognitive functions and quality of life, significant changes were observed in measures of prospective memory ($p < 0.001$), working memory $p = 0.028$, motor speed ($p < 0.001$ and $p = 0.001$), verbal fluency ($p < 0.001$), attention ($p = 0.015$ and $p = 0.019$) and quality of life ($p = 0.042$). See *table 4* for cognitive variables and quality of life (mean, standard deviation and significance).

As concomitant medication was changed during the study period in some patients, we studied the influence of this change on cognitive variables and quality of life. Although slight changes were observed, they were not clinically relevant as comparison of all neuropsychological measures and QoL of patients showed no statistically significant differences when comparing the results of patients whose anti-epileptic treatment remained constant with those whose previous treatment was modified.

Table 5 shows the significance of these results.

As one group of patients had adequate seizure control by the end of the study period and the other did not, we also evaluated the association between seizure control and neuropsychological performance. Data analysis did not show any significant differences in the results of the cognitive and quality of life tests between the two groups. *Table 6* shows results of this analysis.

Discussion

The main findings in this study are that long-term treatment with LEV as add-on therapy has no negative effect on

Table 2. Changes in concomitant medication.

Patient	Treatment at baseline visit (V1)	Treatment at visit 2	Treatment at visit 3	Treatment at visit 4	Treatment at visit 5	Comment
1	VPA 1000 mg				VPA discontinued	After visit 4, VPA was progressively decreased until discontinuation
2	CBZ 1600 mg					No changes
3	VPA 1500 mg			VPA 1000 mg		VPA was decreased after visit 3
4	VPA 2000 mg			VPA 1000 mg		VPA was decreased after visit 3
5	LTG 300 mg					No changes
6	CBZ 1400 mg, CLB 40 mg			CBZ 1200 mg		CBZ was decreased after visit 3
7	CBZ 1200 mg, TGB 30 mg				TGB discontinued	After visit 4, TGB was progressively decreased until discontinuation
8	TPM 400 mg			TPM discontinued	LEV 3000 mg	After visit 3, TPM was progressively decreased until discontinuation, due to nephritic colic. Between visits 4 and 5, LTG 200 mg/day was started. After V4 LEV was increased to 3000 mg/day
9	TPM 600 mg				TPM 400 mg	TPM was decreased after visit 4
10	CBZ 1200 mg, VPA 2500 mg					No changes
11	CBZ 1200 mg					No changes
12	CBZ 1200 mg					No changes
13	PHT 300 mg					No changes
14	CBZ 1200 mg, PHT 300 mg					No changes
15	CBZ 600 mg, GBP 2800 mg	GBP 2000 mg/day LEV 1000 mg/day	GBP 1200 mg/day LEV 2000 mg/day		GBP discontinued	After visit 4, GBP was progressively decreased until discontinuation LEV was increased to 2000 mg/day 2 weeks after visit 2
16	CBZ 1200 mg					No changes
17	CBZ 800 mg, LTG 500 mg				LTG 400 mg	LTG was decreased after visit 4.
18	TPM 400 mg, CLB 20 mg					No changes
19	LTG 600 mg					No changes (LEV 1000 mg the whole period)
20	CBZ 1500 mg				CBZ 1200	CBZ was decreased after V4
21	VPA 2000 mg, LTG 200 mg					No changes
22	VPA 2000 mg, TGB 30 mg					No changes
23	CBZ 1400 mg				CBZ 1200 mg	CBZ was decreased after visit 4
24	VPA 2000 mg			VPA discontinued		After visit 3, VPA was progressively decreased until discontinuation
25	TPM 250 mg, CBZ 1200 mg				TPM discontinued	After visit 4, TPM was progressively decreased until discontinuation
26	CBZ 1500 mg, TGB 45 mg			TGB discontinued	LEV 3000 mg/day	After visit 3, TGB was progressively decreased until discontinuation After visit 4 LEV was increased to 3000 mg/day
27	CBZ 1500 mg					No changes

VPA: valproate; CBZ: carbamazepine; LTG: lamotrigine; CLB: clobazam; TGB: tiagabine; TPM: topiramate; PHT: phenytoin; GBP: gabapentin; LEV: levetiracetam.

Table 3. Mean range of seizures and statistical significance. These values represent the total number of seizures during each period.

	Mean range				
	3 month pre-treatment period	**3 month post-treatment period**	**6 month post-treatment period**	**12 month post-treatment period**	**Significance**
Simple Seizures	2.54	2.41	2.35	2.70	0.523
Complex Seizures	3.31	2.11	2.07	2.50	< 0.001
Secondary Generalized Seizures	2.70	2.44	2.39	2.46	0.088
Generalized Seizures	2.83	2.39	2.41	2.37	0.002

cognitive functions and it improves QoL in patients with refractory epilepsy.

Several studies regarding cognitive functions of LEV have been performed. In one study that assessed cognitive functions such as information processing, memory, attention and speed, no significant changes were observed between pre- and post-treatment evaluations, except for better performance in verbal memory and motor function of the non-dominant hand (Neyens *et al.* 1995). Piazzini *et al.* (2006) compared a LEV-treated group with controls and they observed an improvement in attentional functions and verbal fluency. Zhou *et al.* (2008) assessed LEV as add-on therapy and found an improvement in some neuropsychological measurements in the patient group after

Table 4. Cognitive variables and quality of life.

	Mean ± standard deviation					
Variable	**Baseline**	**1 month**	**3 months**	**6 months**	**12 months**	**Significance**
Prospective Memory	7.52 ± 2.01	8.85 ± 1.99	9.07 ± 1.88	8.89 ± 1.78	9.52 ± 2.19	< 0.001
Rey 1	4.96 ± 1.40	5.59 ± 1.89	6.30 ± 2.07	5.44 ± 1.74	5.78 ± 1.63	0.025
Rey 2	7.22 ± 2.03	7.59 ± 2.15	8.19 ± 2.25	8.11 ± 2.15	7.96 ± 2.23	0.081
Rey 3	8.85 ± 2.11	9.41 ± 2.14	9.74 ± 1.97	9.33 ± 2.48	9.33 ± 2.42	0.266
Rey 4	10.11 ± 2.06	10.44 ± 2.22	10.74 ± 2.07	10.48 ± 2.36	10.78 ± 2.21	0.347
Rey 5	11.26 ± 2.35	10.89 ± 1.99	11.22 ± 3.14	11.41 ± 2.31	11.19 ± 2.48	0.795
Rey Long Term	8.78 ± 2.94	8.23 ± 2.80	8.15 ± 3.64	9.00 ± 2.84	9.19 ± 3.01	0.219
WAIS (Letters and numbers)	8.00 ± 2.54	8.33 ± 2.37	9.22 ± 2.47	8.85 ± 1.96	8.85 ± 2.09	0.028
VRT	12.70 ± 1.54	13.07 ± 1.84	12.78 ± 1.28	12.78 ± 1.69	13.15 ± 1.46	0.433
CPT (correct answers)	40.41 ± 4.77	41.52 ± 4.21	41.00 ± 4.22	41.11 ± 4.29	41.89 ± 3.30	0.399
Purdue Pegboard Test Right Hand	12.63 ± 1.78	13.15 ± 2.18	13.26 ± 2.09	13.52 ± 2.64	14.11 ± 2.15	< 0.001
Purdue Pegboard Test Left Hand	12.37 ± 1.94	12.33 ± 1.92	12.85 ± 1.63	12.85 ± 1.90	12.93 ± 1.62	0.175
Purdue Pegboard Test Both Hands	19.78 ± 2.83	20.67 ± 6.55	20.63 ± 3.51	20.81 ± 3.63	21.30 ± 3.00	0.435
Purdue Pegboard Test Assembly	29.22 ± 6.19	27.19 ± 7.08	27.33 ± 7.37	29.26 ± 7.51	31.30 ± 7.65	0.001
Verbal Fluency	10.48 ± 3.48	9.44 ± 3.57	9.33 ± 3.67	12.70 ± 3.88	11.11 ± 3.95	< 0.001
Trail Making Test B Mistakes	2.04 ± 3.46	0.62 ± 1.24	0.23 ± 0.82	0.50 ± 0.95	0.38 ± 0.70	0.015
Trail Making Test B Time	173.08 ± 105.69	139.27 ± 75.20	145.19 ± 51.10	128.15 ± 100.56	114.38 ± 55.67	0.019
Stroop Denomination Mean Time	961.907 ± 239.36	928.130 ± 224.05	936.287 ± 229.97	914.567 ± 203.22	875.920 ± 195.33	0.078
Stroop Denomination Mean Mistakes	0.38 ± 0.75	0.08 ± 0.27	0.35 ± 0.56	0.35 ± 0.49	0.31 ± 0.47	0.163
Stroop Interference Mean Time	1272.912 ± 713.35	1233.414 ± 1136.59	1027.158 ± 311.25	970.48 ± 255.61	942.939 ± 210.59	0.131
Stroop Interference Mean Mistakes	0.35 ± 0.56	0.35 ± 0.80	0.23 ± 0.51	0.12 ± 0.43	0.23 ± 0.51	0.499
QOLIE-31	61.9074 ± 13.32	64.7474 ± 14.46	68.3119 ± 15.31	69.6422 ± 13.46	69.3448 ± 14.16	0.042

WAIS: Wechsler Adult Intelligence Scale; VRT: Visual Retention Test; CPT: Continuous Performance Test; QOLIE: Quality-of-Life-in-Epilepsy Inventory.

Table 5. Significance of the comparison between the group of patients who remained on stable concomitant treatment and those who did not. Only principal variables are presented.

		Mean ± standard deviation					
Variable		**Baseline**	**1 month**	**3 months**	**6 months**	**12 months**	**Significance**
Prospective Memory	No change	7.15 ± 1.8	9.15 ± 1.2	9.46 ± 1.2	8.85 ± 1.2	9.54 ± 1.5	0.178
	Change	7.86 ± 2.1	8.57 ± 2.5	8.71 ± 2.3	8.93 ± 2.2	9.50 ± 2.7	
WAIS (Letters - numbers)	No change	8.08 ± 2.3	8.92 ± 1.7	9.69 ± 2.4	9.08 ± 2.0	9.08 ± 2.0	0.771
	Change	7.93 ± 2.7	7.79 ± 2.7	8.79 ± 2.4	8.64 ± 1.9	8.64 ± 1.9	
PPT Right Hand	No change	12.69 ± 1.3	13.08 ± 2.5	13.38 ± 2.3	13.23 ± 3.0	14.08 ± 2.5	0.717
	Change	12.57 ± 2.1	13.21 ± 1.8	13.14 ± 1.8	13.79 ± 2.3	14.14 ± 1.8	
PPT Assembly	No change	29.08 ± 6.9	28.54 ± 7.5	29.15 ± 7.1	30.77 ± 6.8	32.62 ± 8.3	0.355
	Change	29.36 ± 5.6	25.93 ± 6.6	29.64 ± 7.4	27.86 ± 8.0	30.07 ± 7.0	
Verbal Fluency	No change	10.38 ± 3.0	9.77 ± 2.9	9.92 ± 4.0	13.00 ± 4.0	10.62 ± 4.4	0.426
	Change	10.57 ± 3.9	9.14 ± 4.1	8.79 ± 3.3	12.43 ± 3.8	11.57 ± 3.5	
TMT B Mistakes	No change	3.00 ± 4.0	0.85 ± 1.5	0.46 ± 1.1	0.38 ± 0.9	0.46 ± 0.8	0.201
	Change	1.08 ± 2.4	0.38 ± 0.8	0.00 ± 0	0.62 ± 0.9	0.31 ± 0.4	
TMT B Time	No change	180 ± 104	131.1 ± 52	144 ± 58	121 ± 110	108 ± 39	0.776
	Change	166 ± 111	147.2 ± 95	146 ± 46	135 ± 94	121 ± 70	
QOLIE-31	No change	± 14	61.2 ± 11.4	62.8 ± 13.8	64.6 ± 12.9	69.0 ± 14.4	0.355
	Change	64.7 ± 12.7	68.0 ± 16.5	73.4 ± 15.2	74.2 ± 12.6	69.5 ± 14.3	

PPT: Purdue Pegboard Test; TMT: Trail Making Test; WAIS: Wechsler Adult Intelligence Scale; QOLIE: Quality-of-Life-in-Epilepsy Inventory.

short-term treatment. These changes remained stable at long-term evaluation.

Other authors have recently compared LEV with other AED. Gomer *et al.* (2007) found a significant deterioration with topiramate, but no impairment of cognitive function in patients treated with LEV. They even noted an improvement in attentional functions, further contributing to the generally reported, good tolerability of the drug. Ciesielski *et al.* (2006) compared pregabalin with LEV and they found no significant changes in cognitive functions between groups in a short-term follow up of seven days, but they did find a significant improvement in visual short-

Table 6. Analysis between the group of patients who had controlled seizures and those who did not. In this table, the results of the principal variables are shown.

		Mean ± standard deviation					
Variable		**Baseline**	**1 month**	**3 months**	**6 months**	**12 months**	**Significance**
Prospective Memory	Controlled	7.53 ± 1.6	9.00 ± 1.4	9.37 ± 1.3	9.05 ± 1.2	9.58 ± 2.1	0.675
	Uncontrolled	7.50 ± 2.8	8.50 ± 3.0	8.38 ± 2.7	8.50 ± 2.7	9.38 ± 2.5	
WAIS (Letters - numbers)	Controlled	8.05 ± 2.3	8.37 ± 2.2	9.74 ± 2.5	9.11 ± 1.9	8.74 ± 1.9	0.128
	Uncontrolled	7.88 ± 2.3	8.25 ± 2.8	8.00 ± 2.0	8.25 ± 1.9	9.13 ± 1.9	
PPT Right Hand	Controlled	12.89 ± 1.8	13.42 ± 2.3	13.47 ± 2.4	13.58 ± 3.1	14.37 ± 2.4	0.758
	Uncontrolled	12.00 ± 1.8	12.50 ± 1.5	12.75 ± 0.7	13.38 ± 0.9	13.50 ± 1.3	
PPT Assembly	Controlled	29.89 ± 6.4	27.95 ± 7.6	28.47 ± 7.8	29.32 ± 7.6	32.42 ± 8.4	0.433
	Uncontrolled	27.63 ± 5.7	25.38 ± 5.5	24.63 ± 5.6	29.13 ± 7.6	28.63 ± 4.5	
Verbal Fluency	Controlled	11.00 ± 3.4	9.68 ± 3.3	9.32 ± 3.7	12.68 ± 3.6	10.79 ± 3.9	0.255
	Uncontrolled	9.25 ± 3.4	8.88 ± 4.1	9.38 ± 3.6	12.75 ± 4.6	11.88 ± 4.1	
TMT B Mistakes	Controlled	1.84 ± 3.5	0.53 ± 0.9	0.16 ± 0.6	0.42 ± 1.0	0.21 ± 0.4	0.832
	Uncontrolled	2.57 ± 3.3	0.86 ± 1.8	0.43 ± 1.1	0.71 ± 0.7	0.86 ± 1.0	
TMT B Time	Controlled	161 ± 86	127.3 ± 42	141 ± 53	135 ± 115	115 ± 62	0.196
	Uncontrolled	204 ± 43	171.3 ± 128	154 ± 46	107 ± 41	110 ± 36	
QOLIE-31	Controlled	61.3 ± 12.0	63.2 ± 12.2	67.6 ± 14.0	69.5 ± 12.4	69.8 ± 10.5	0.756
	Uncontrolled	63.1 ± 16.8	68.3 ± 19.3	69.9 ± 18.8	69.9 ± 16.6	68.2 ± 21.3	

PPT: Purdue Pegboard Test; TMT: Trail Making Test; WAIS: Wechsler Adult Intelligence Scale; QOLIE: Quality-of-Life-in-Epilepsy Inventory.

term memory in the LEV group. On comparing LEV and carbamazepine as monotherapy in healthy subjects, Meador *et al.* (2007) observed fewer neuropsychological side effects with the former.

Our results agree with those of previous investigations describing an improvement in several cognitive areas. We observed better performance in prospective and working memory, motor speed, verbal fluency and attention in our group of patients.

The treatment period varies greatly in these studies, ranging from a few weeks in the studies by Ciesielski *et al.* (2006) and Neyens *et al.* (1995), to 24 weeks after titration in the study by Zhou *et al.* (2008). Our study reports the longest treatment period to date, 11 months after one month titration. Bearing in mind that a five-week period is sufficient to obtain stable anti-epileptic blood levels (Meador *et al.* 1999), the present study provides additional information regarding the long-term effects of LEV treatment on the cognitive profile.

As well as changes in some cognitive functions, improvement in quality of life was observed in our study group after the year of treatment. These findings correlate with those of Cramer *et al.* (Cramer *et al.* 2000), where patients showed an improved quality of life after 18 weeks of treatment and also after long-term treatment (Cramer and Van Hammee 2003).

In the present study, the significant changes seen in neuropsychological variables and quality of life did not differ between the group of patients whose previous anti-epileptic treatment remained unchanged and the group whose prior treatment was changed. This suggests that improvement in these aspects is not due to a decrease or discontinuation of the concomitant medication, and supports data concerning the absence of adverse effects of LEV on cognition and quality of life. Nevertheless, the results may be due to the sample size.

Regarding efficacy of treatment, at the end of the twelve-month follow-up period, complex and generalized seizures showed a significant improvement and there was a decrease in the number of secondary generalized seizures. However, this improvement was not statistically significant. The number of simple seizures increased during the follow-up, but we consider that this can be explained by the fact that patients who had complex and generalized seizures experienced a reduction in the number of such seizures but showed an increase in simple seizures. The reduction of complex and generalized seizures was described by the patients as an improvement, because they felt less disabled and this allowed them to have a better quality of life. Although the sample may not be large enough to assess these changes, seizure reduction did not appear to influence neuropsychological performance.

Other authors have assessed aspects such as cognitive effects of AED (Fritz *et al.* 2005, Blum *et al.* 2006), but our report simultaneously studies the effects of LEV on cognitive functions, quality of life and seizure frequency in the same group of patients and over a longer period of time. This general view further supports the evidence regarding a long-term lack of adverse effects of LEV treatment at a total daily dose of 2000 mg.

One methodological limitation of the present study could be the lack of a control group. This would likely have been useful in determining learning and placebo effects, but in our clinical practice it was difficult to establish a group of patients with comparable educational levels, treatment, cognitive status, and number of seizures. It should also be pointed out that although the sample size was limited, the long follow-up period provided interesting information regarding the long-term effects of treatment, and may help in decision-making when choosing an adjunctive treatment for patients with partial complex seizures, with or without secondary generalization.

We consider that data obtained from this study could be useful for daily clinical practice, as factors that may affect cognitive functions and QoL, such as seizure frequency and changes in concomitant anti-epileptic treatment, were also studied.

In conclusion, the results of this prospective study suggest that long-term treatment with the anti-epileptic drug LEV does not interfere with cognitive function, improves quality of life and also reduces seizure frequency. These findings need to be replicated in larger samples. □

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