

Levetiracetam Effectiveness as Add-on Therapy in Bulgarian Patients with Drug-Resistant Epilepsy

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Abstract

Introduction: There are no reliable prospective studies on the effectiveness of LEV in Bulgarian adult patients with drug-resistant epilepsy.

Aim: The study aimed at conducting an open, prospective study on various aspects of levetiracetam (LEV) effectiveness in Bulgarian patients with drug-resistant epilepsy.

Materials and methods: The study was performed with patients with epilepsy recruited from those attending the Department of Neurology at the University Hospital in Plovdiv, Bulgaria. The patients completed diaries about seizure frequency, severity, and adverse events. There were regular documented visits at 3 or 6 months during the first year of treatment with LEV and at 6 months afterwards, with dynamic assessment of seizure frequency, severity, adverse events, and EEG recordings.

Results: LEV was applied as an add-on therapy in 135 patients (86 males, mean age 35 years). There was a relatively mild and persisting dynamic improvement of seizure severity, a satisfactory seizure frequency reduction in 49.6% of participants, a persisting mean seizure frequency reduction (48-58%) from 6 to 36 months of treatment and a high responder rate (53-60%) during the same period. New seizure types (focal with impaired awareness with /without evolution to bilateral tonic-clonic seizures) occurred in 4 patients. There were adverse events (dizziness, memory impairment, aggressiveness, numbness, non-epileptic seizures, depression, anxiety, speech disturbances, visual hallucinations, sleepiness, pelvic muscles weakness, confusion, sleep disturbances, loss of appetite, unstable gait, hair loss, acne, generalized rash) in 13.33% of patients.

Conclusions: LEV treatment is associated with: low and persisting improvement of seizure severity, a good and persisting improvement of seizure frequency, a possible worsening of seizure control, a possible appearance of new seizure types, a good safety and tolerability.

Keywords

adverse events, efficacy, epilepsy, levetiracetam, tolerability

INTRODUCTION

Levetiracetam (LEV) is a newer generation antiepileptic drug (AED) which has been confirmed as an appropriate drug for monotherapy and add-on therapy in patients

with newly diagnosed focal seizures with impaired awareness with/without evolution to bilateral tonic-clonic seizures and add-on therapy in patients with juvenile myoclonic epilepsy and with generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy. The favour-

rable pharmacokinetics, lack of drug interactions and enzyme induction activity, as well as rare and mild adverse events, have been proven as other advantages explaining the frequent usage of LEV in medical practice.¹⁻⁹ There are no reliable prospective studies on effectiveness of LEV in Bulgarian adult patients with drug-resistant focal seizures with impaired awareness with/without evolution to bilateral tonic-clonic seizures. Therefore, the conduction of an open, prospective study on various aspects of effectiveness of add-on therapy with LEV in Bulgarian patients with drug-resistant epilepsy will provide additional useful data for the medical practice.

AIM

To perform an open, prospective study on various aspects of LEV effectiveness in Bulgarian patients with drug-resistant epilepsy.

PATIENTS AND METHODS

The study is open, prospective, with the participation of patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria for a regular examination in cases of unsatisfactory seizure control or for adverse events from treatment. All study procedures were performed after the approval of the Local Ethics Commission at the Medical University, Plovdiv. Every patient was introduced to the study design and signed an informed consent form before participating in the study procedures. The following inclusion criteria were used: 1. Age > 18 years; 2. Good compliance of patients to recommended treatment; 3. A stable dose of concomitant AEDs in the recent 3 months; 4. Completed diary about seizure frequency, severity, and adverse events; The criteria for AEDs choice are in conformity with the indications approved by the National Drug Agency.

Data were processed using STATA (Stata Corp., College Station, TX, USA) and SPSS (Statistical Package for the Social Sciences) version 19.0 (SPSS Inc., Chicago, IL, USA). The results for quantitative variables were expressed as means \pm SE (standard error) and the results for qualitative variables – as percentages. The principal outcomes were: clinical efficacy (seizure frequency and severity reduction, modification of seizure type, duration of LEV effectiveness, retention rate of patients, reasons for termination of LEV treatment) and tolerability (manifestation of adverse events). The assessment of seizure frequency dynamics included: worsening, no change, reduction <50%, reduction >50%, reduction 100%. Patients with seizure frequency reduction of at least 50% were accepted as responders to treatment, while those with seizure frequency less than 50% were considered as being with minimal efficacy on the seizure frequency control. The assessment of seizure severity dynamics included worsening, no change and improvement of the following characteristics: seizure duration, duration of the loss of consciousness, traumatism, and postictal manifestations. The association of dynamics in seizure frequency and severity with demographics (age, gender), and clinical findings was tested by means of χ^2 -test and F-test. The level of significance was set at $p < 0.05$.

RESULTS

LEV was applied in 135 patients (86 males) of 18-63 years of age (mean age 35.6 ± 1.1). The onset of epilepsy varied from 1 month to 57 years of age, mean age of onset 16.8 ± 1.0 years. The mean epilepsy duration varied from 2 to 51 years (mean epilepsy duration, 29.4 ± 2.1 years). The observation continued from 10 days to 108 months (mean duration 29.4 ± 0.4 months). The most common dosage of LEV was 2000 mg/d (mean dosage 1892 ± 1.8 mg/d). The demographic and clinical characteristics of study participants are presented in **Table 1**.

Table 1. Demographic and clinical characteristics of patients on treatment with LEV

Characteristics	N	P (%)	SE
Gender			
– males	86	63.7	4.15
– females	49	36.3	4.15
Age at baseline (years)			
– < 25	33	24.4	3.71
– 26-35	36	26.7	3.82
– 36-45	34	25.2	3.75
– > 45	32	23.7	3.67
Age at epilepsy onset			
– < 18 years	92	68.15	4.02
– > 18 years	43	31.85	4.02
Epilepsy duration			
– < 10 years	40	29.63	3.94
– > 10 years	95	70.37	3.94

Study duration (months)			
– < 6	3	2.2	–
– 6	20	14.8	3.07
– 12	36	26.7	3.82
– 24	22	16.3	3.19
– 30-36	21	15.6	3.13
– 48	13	9.6	2.54
– 54-60	7	5.2	1.92
– 72	5	3.7	1.63
– 84	3	2.2	–
– 96	1	0.7	–
– 108	3	2.2	–
Seizure type			
– focal without impaired awareness	1	0.7	–
– focal with impaired awareness	1	0.7	–
– focal with evolution to bilateral tonic-clonic seizures	56	41.5	4.26
– generalized tonic-clonic seizures	27	20.0	3.46
– generalized atonic seizures	2	1.5	–
– focal and generalized seizures	48	35.6	4.14
Type of epilepsy			
– focal	90	66.6	4.07
– generalized	45	33.4	4.07
Etiology of epilepsy			
– genetic	9	6.7	2.16
– structural/metabolic (traumatic, vascular, inflammatory, tumor, perinatal pathology, hippocampal sclerosis, brain malformations, tuberous sclerosis, multiple sclerosis)	62	45.9	4.30
– unknown	64	47.4	4.31
Concomitant diseases			
– no	88	65.2	4.12
– somatic	26	19.3	3.41
– psychiatric	13	9.6	2.54
– neurological	8	5.9	2.04
Seizure clusters and/or status epilepticus in the disease course			
– yes	55	40.7	4.24
– no	80	59.3	4.24
Cognitive functions			
– normal	118	87.4	2.87
– mental retardation/ cognitive deficit	17	12.6	2.87
Neurological status			
– normal	107	79.3	.50
– with focal neurological signs	28	20.7	3.50
Recent seizure frequency			
– 1-11 seizures/ year	15	11.1	2.71
– 1-3 seizures/ month	35	25.9	3.78
– 1-6 seizures/ week	60	44.4	4.29
– daily	25	18.6	3.36
Recent seizure severity			
– mild	18	13.3	2.93
– severe	117	86.7	2.93
AED treatment at study onset			
– monotherapy	59	43.7	4.28
– polytherapy	76	56.3	4.28
Initial LEV dosage			
– 1000 mg/d	7	5.2	1.92
– 1500 mg/d	36	26.7	3.82

– 2000 mg/d	81	60.0	4.23
– 2750 mg/d	1	0.7	–
– 3000 mg/d	10	7.4	2.26
Concomitant AEDs			
– VPA 1000-2000 mg/d	29	21.5	3.55
– CBZ 400-1000 mg/d	8	5.9	2.04
– CZP 1-2 mg/d	2	1.5	–
– PHT 100-200 mg/d	2	1.5	–
– OCBZ 900-1800 mg/d	10	7.4	2.26
– LTG 200 mg/d	1	0.7	–
– TPM 300-350 mg/d	2	1.5	–
– VPA 1000-2000 mg/d + CBZ 600-800 mg/d	13	9.6	2.54
– VPA 1000-2000 mg/d + OCBZ 600-1800 mg/d	26	19.3	3.41
– VPA 1250-2000 mg/d + CZP 1.5-4 mg/d	2	1.5	–
– VPA 1000-2000 mg/d + TPM 200-300 mg/d	9	6.7	2.16
– VPA 900-1500 mg/d + LTG 150-300 mg/d	5	3.7	1.63
– VPA 1500 mg/d + TGB 20 mg/d	1	19.3	–
– VPA 1250 mg/d + PGB 600 mg/d	1	0.7	–
– CBZ 600 mg/d + CZP 1-6 mg/d	2	1.5	–
– CBZ 1000 mg/d + GBP 2000 mg/d	1	0.7	–
– CBZ 700 mg/d + TPM 50 mg/d	1	0.7	–
– CZP 1-1.5 mg/d + OCBZ 1200-1800 mg/d	2	1.5	–
– CZP 2 mg/d + LTG 300 mg/d	1	0.7	–
– OCBZ 1200-1800 mg/d + LTG 300 mg/d	2	1.5	–
– OCBZ 1800 mg/d + PGB 600 mg/d	1	0.7	–
– PGB 600 mg/d + TGB 60 mg/d	1	0.7	–
– OCBZ 1800 mg/d + TGB 30 mg/d	1	0.7	–
– CZP 3 mg/d + TPM 300 mg/d	1	0.7	–
– TPM 300 mg/d + LTG 300 mg/d	1	0.7	–
– TPM 300 mg/d + OCBZ 1800 mg/d	1	0.7	–
– TPM 300 mg/d + PGB 600 mg/d	1	0.7	–
– VPA 1500 mg/d + CBZ 600 mg/d + CZP 4 mg/d	1	0.7	–
– VPA 1500 mg/d + TPM 350 mg/d + PGB 300 mg/d	1	0.7	–
– VPA 1250 mg/d + OCBZ 1200 mg/d + GBP 1200 mg/d	1	0.7	–
– PHT 200 mg/d + VPA 2000 mg/d + CBZ 600 mg/d	1	0.7	–
– OCBZ 1800 mg/d + LTG 300 mg/d + CZP 2 mg/d	1	0.7	–
– VPA 1500 mg/d + CBZ 600 mg/d + Diazepam 20 mg/d	1	0.7	–
– VPA 2000 mg/d + CBZ 800 mg/d + TPM 300 mg/d	1	0.7	–
– VPA 1500 mg/d + TPM 250 mg/d + TGB 40 mg/d	1	0.7	–
EEG at the study onset			
– normal	66	48.9	4.32
– focal activity	44	32.6	4.05
– generalized paroxysmal activity	2	1.5	–
– diffuse slow-wave activity	4	3.0	–
– diffuse epileptiform activity	2	1.5	–
– scattered abnormalities, no focus formation	9	6.7	2.16
– focal + diffuse findings	8	5.9	2.04

* VPA: valproate; CBZ: carbamazepine; PHT: phenytoin; PB: phenobarbital; OCBZ: oxcarbazepine; TPM: topiramate, GBP: gabapentin; CZP: clonazepam, LTG: lamotrigine; LEV: levetiracetam; PGB: pregabalin; TGB: tiagabine

We did not find significant difference in the percentage of patients without improvement of seizure severity up to 36 months of treatment. The percentage of participants with seizure severity reduction persisted between the 6th

and 36th months (25.4% at 6 months, 26.4% at 12 months, 31.5% at 24 months, 25% at 36 months). Because of the small number of patients who continued LEV treatment after the 36th month, they were not included in the statisti-

cal analysis. We came to the conclusion about a mild and persisting improvement of seizure severity by treatment with LEV.

The seizure severity improvement correlated with the initial seizure frequency ($p < 0.05$, $r = -0.217$) and seizure frequency dynamics ($p < 0.01$, $r = 0.69$) at 6 months of treatment. Seizure severity improvement was most frequent in patients with high initial seizure frequency – in 20 (34.5%) of those with high weekly frequency and 7 (28%) of those with daily seizures.

The assessment of seizure frequency up to the 36th month of LEV treatment is presented in **Table 2**.

Table 2. Seizure frequency assessment during treatment with LEV

	Seizure frequency dynamics				Total N (p%)
	No change N (p%)	Reduction 50-99% N (p%)	Reduction 100% N (p%)	Increase N (p%)	
6 months	54 (40.9%)	46 (34.8%)	24 (18.2%)	8 (6.1%)	132 (100.0%)
12 months	41 (37.3%)	42 (38.1%)	20 (18.2%)	7 (6.4%)	110 (100.0%)
24 months	22 (29.4%)	30 (40.0%)	13 (17.3%)	10 (13.3%)	75 (100.0%)
36 months	16 (30.2%)	18 (34.0%)	14 (26.4%)	5 (9.4%)	53 (100.0%)

The most significant improvement of seizure frequency was found at 6 months of treatment followed by retention of a high responder rate of about 55-60% (53% at 6 months, 56.4% at 12 months, 57.3% at 24 months, and 60.4% at 36 months) and gradual increase of the percentage of patients without seizures up to 26.4% (**Table 2**). There was also gradual increase of participants with seizure frequency increase – up to 13.3% at 24 months followed by decrease to 9.4% at 36 months (**Table 2**). The statistical analysis of results confirmed that there was no significant decrease in seizure frequency between the 6th and 12th months and between the 6th and 24th months ($p > 0.05$, $\chi^2 = 0.31$, Friedman test). We found the following dynamics in the mean seizure frequency reduction – 48% at 6 months, 51% at 12 months, 57% at 24 months, and 58% at 36 months. Therefore, regarding seizure frequency, the efficacy of LEV was good and persisting for the study period.

The seizure frequency dynamics correlated with the initial seizure frequency at 6 months ($p < 0.05$, $\chi^2 = 10.71$; $r = -0.178$) and at 24 months of study ($p > 0.05$, $\chi^2 = 8.08$), ($p = 0.052$, $r = 0.35$). At 6 months, the seizure frequency increase was more common in patients with low initial frequency, while at 24 months the seizure frequency improvement was more frequent in patients with low initial seizure frequency. The final seizure frequency reduction correlated with initial mono- or polytherapy ($p < 0.05$, $r = -0.21$) and with seizure clusters and/or status epilepticus in the disease course ($p < 0.05$, $r = 0.31$). Most seizure free participants (62.5%) and 52.24% of responders were with initial monotherapy. Most seizure free patients (87%) and 71.64% of the responders did not have seizure clusters and/or status epilepticus in the disease course.

There was a modification of the seizure type in a small number of patients – manifestation of focal seizures with impaired awareness without evolution to bilateral tonic-clonic seizures in 3 patients with GTCS at 6 months of study and in 1 patient at 36 months of study.

In 26 (19.3%) study participants LEV treatment was terminated for various reasons: 1. Adverse events from treatment – in 5 (3.7%) patients; 2. Lack of efficacy, transient efficacy or increased seizure frequency – in 8 (5.9%) patients; 3. A combination of adverse events and lack of efficacy – 4 (3%). After taking into consideration the drop-out patients, we found gradual decrease of the percentage of

patients continuing LEV treatment, i.e. the retention rate was 95.56% at 6 months, 91.13% at 12 months, 86% at 24 months, 83.8% at 36 months, and 80.73% at 48 months.

The total duration of LEV treatment was 3945 months. The total duration of effectiveness was 2486 months, therefore LEV was effective in 63.02% of the treatment time of all patients. The mean effectiveness duration was 30.32 ± 0.44 months. The effectiveness duration is presented in **Table 3**.

Table 3. Duration of LEV effectiveness

Effectiveness	Number of patients (N)	p%	SE
Worsening	8	6.0	2.06
No effect	44	32.8	4.07
3 months	1	0.7	–
6 months	17	12.7	2.89
12 months	17	12.7	2.89
18 months	3	2.2	–
24 months	11	8.2	2.38
30 months	2	1.5	–
36 months	9	6.7	2.17
47 months	1	0.7	–
48 months	6	4.5	3.23
54 months	2	1.5	–
60 months	4	3.0	–
72 months	4	3.0	–
84 months	1	0.7	–
96 months	1	0.7	–
108 months	3	2.2	–
Total	134	100.0	

Safety and tolerability of LEV treatment

There were adverse events from treatment in 18 (13.33%) of study participants (Table 4). We did not confirm a correlation of adverse events with demographic and clinical factors.

These results could not be compared with other studies for the lack of literature data. The described above satisfactory seizure frequency reduction in 49.6% of participants (17.8% seizure free), the persisting mean seizure frequency reduction (48-58%) from the 6th to the 36th month of study, as well as the high responder rate (53-60.4%) during

Table 4. Adverse events from LEV treatment

Adverse event	Number of patients	Dosage (mg/d)	Severity	LEV termination	Duration of AE
Dizziness	1	1500	Moderate	No	540 days
	1	2000	Moderate	Decreased dose and terminated	360 days
Memory impairment	1	2000	Moderate	Decreased dose and terminated	360 days
	1	2000	Moderate	No	330 days
	1	2000	Mild	No	600 days
	1	2000	Mild-severe	Yes	270 days
Aggressiveness	1	2000	Severe	Yes	30 days
	1	2000	Moderate -severe	Yes	270 days
Numbness	1	2000	Moderate	Decreased dose and terminated	360 days
	1	2000	Moderate	No	330 days
Non-epileptic seizures	1	2000	Moderate	No	180 days
Depression	1	2000	Moderate -severe	Yes	270 days
Anxiety	1	1500	Moderate	No	540 days
	1	2000	Moderate-severe	Yes	270 days
Speech disturbances	1	2000	Severe	Yes	90 days
Visual hallucinations	1	2000	Moderate	No	340 days
Sleepiness	1	2000	Severe	Yes	30 days
	1	2000	Mild-severe	Yes	270 days
Pelvic muscles weakness	1	2000	Moderate	No	150 days
Confusion	1	2000	Moderate	No	330 days
Sleep disturbances – night-mares, sleep talking	1	1500	Moderate	No	60 days between 6 th and 12 th month
Loss of appetite	1	2000	Moderate	No	150 days
Unstable gait	1	2000	Severe	Yes	10 days
Hair loss	1	2000	Moderate	Yes	330 days
Acne	1	2000	Moderate	No	330 days
Generalized rash	1	2000	Severe	Yes	10 days

DISCUSSION

In our study, LEV was applied as an add-on treatment in 135 patients of mean age 36 years with drug-resistant focal or a combination of focal and generalized tonic-clonic seizures. There was relatively mild and persisting dynamic improvement of seizure severity, which correlated with the initial seizure frequency and seizure frequency dynamics.

the same period, are similar to the results reported in literature from double-blind, randomized studies, and to those from some open prospective studies¹⁻⁶, with the exception of lacking dose-dependent effect reported by some investigators.⁷⁻⁹ Seizure frequency improvement correlated with initial monotherapy and the lack of seizure clusters and/or status epilepticus in the disease course. Investigators have not focused attention on the percentage of patients with

worsened seizure control during LEV treatment, probably because of the uncertain association with drug intake in all patients. The percentage of our study participants with worse seizure control, without improvement or minimal efficacy, is not a small one (15.6% and 34.8%, respectively), and suggests focusing attention in future studies, moreover the lack of efficacy is the reason for LEV treatment termination in 8.9% of study participants.

The appearance of new seizure types in 4 patients suggests the question whether this phenomenon is associated with some of its mechanisms of action or is a result of the disease course. There are no similar data and a discussion of this problem in literature.

There was a gradual decrease of the percentage of patients continuing LEV treatment from 95.56% at 6 months to 83.8% at 36 months. We found only one study with 1142 patients in literature focusing attention on retention rate of LEV. Krakow et al.¹⁰ reported significantly higher and quicker decrease of LEV retention rate – from 60% at the end of the first year to 32% after the 5th year. Predictors of a higher retention rate were: higher maximum dose, low initial dose, generalized tonic-clonic seizures, a smaller number of concomitant AEDs at the onset of LEV treatment.¹¹

LEV showed good safety and tolerability in our study participants. The frequency of reported adverse events (13.3%) was similar to that in the literature data, they were usually with moderate severity and became a cause of treatment termination in a similar percentage of patients (6.7%).^{1-4,12} Unusual adverse events were found in 15 patients – memory impairment, numbness, speech disturbances, pelvic muscles weakness, nightmares, unstable gait, hair loss, skin problems. They could result in LEV termination and necessitate attention for the possibility of manifestation in the medical practice. Most adverse events were similar to the ones reported in literature and were not associated with a higher LEV dose.^{1-3,5,6,12,14-20}

CONCLUSIONS

The results from our study suggest the following advantages of LEV treatment: low and persisting improvement of seizure severity, good and persisting reduction of seizure frequency, a possibility of worsening of seizure control, possible appearance of new seizure types, good safety and tolerability.

REFERENCES

1. Lambrechts DA, Sadzot B, van Paesschen W, et al. Efficacy and safety of levetiracetam in clinical practice: results of the SKATE trial from Belgium and the Netherlands. *Seizure* 2006; 15(6):434–42.
2. Steinhoff BJ, Trinka E, Wieser HG, DACH-LEV Study Group. Levetiracetam in patients with refractory epilepsy: results of the SKATE trial in Austria, Germany and Switzerland. *Seizure* 2005; 14(7):490–6.
3. Steinhoff BJ, Somerville ER, Van Paesschen W, et al. The SKATE study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. *Epilepsy Res* 2007; 76(1):6–14.
4. Somerville ER, McLaughlin DB, Robinson MK, et al. Adjunctive therapy of uncontrolled partial seizures with levetiracetam in Australian patients. *Epilepsy Behav* 2007; 11(3):338–42.
5. Kwan P, Lim SH, Chinvarun Y, et al, N01036 (SKATE II) Investigator group. Efficacy and safety of levetiracetam as adjunctive therapy in adult patients with uncontrolled partial epilepsy: the Asia SKATE II Study. *Epilepsy Behav* 2010; 18(1-2):100–5.
6. Abou-Khalil B, Schaich L. Long-term efficacy of levetiracetam for partial seizures. *Seizure* 2005; 14(8):577–85.
7. Ben-Menachem E, Flater U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000; 41:1276–83.
8. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000; 55:236–42.
9. Shorvon SD, Lowenthal A, Janz D, et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 2000; 41:1179–86.
10. Krakow K, Walker M, Otoul C, et al. Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology* 2001; 56(12):1772–4.
11. Ben-Menachem E, Gilland E. Efficacy and tolerability of levetiracetam during 1-year follow-up in patients with refractory epilepsy. *Seizure* 2003; 12:131–5.
12. Bauer J, Ben-Menachem E, Kramer G, et al. Levetiracetam: A long-term follow-up study of efficacy and safety. *Acta Neurol Scand* 2006; 114:169–76.
13. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 2000; 9:80–7.
14. Tsai JJ, Yen DJ, Hsieh MS, et al. Efficacy and safety of levetiracetam (up to 2000 mg/day) in Taiwanese patients with refractory partial seizures: a multicenter, randomized, double-blind, placebo-controlled study. *Epilepsia* 2006; 47(1):72–81.
15. Salas-Puig J, Serratosa JM, Viteri C, et al. Grupo Espanol del Estudio SKATE. Safety of levetiracetam as adjunctive therapy in epilepsy: the SKATE trial in Spain. *Rev Neurol* 2004; 38(12): 1117–22.
16. Abou-Khalil B, Hemdal P, Privitera MD. An open-label study of levetiracetam at individualised doses between 1000 and 3000 mg day in adult patients with refractory epilepsy. *Seizure* 2003; 12(3):141–9.
17. Weintraub D, Buchsbaum R, Spencer HT, et al. Tolerability of levetiracetam in 516 patients; analysis by dose and serum concentration. *Epilepsia* 2004; 45(suppl 3):68.
18. Youroukos S, Lazopoulou D, Michelakou D, et al. Acute psychosis associated with levetiracetam. *Epileptic Disord* 2003; 5:117–19.
19. Dinkelacker V, Dietl T, Widman G, et al. Aggressive behaviour of epilepsy patients in the course of levetiracetam add-on therapy; report of 33 mild to severe cases. *Epilepsy Behav* 2003; 4:537–47.
20. Brodtkorb E, Klees TM, Nakken KO, et al. Levetiracetam in adult patients with and without learning disability: focus on behavioural adverse effects. *Epilepsy Behav* 2004; 5(2):231–5.

Эффективность леветирацетама в качестве дополнительной терапии у болгарских пациентов с лекарственно-устойчивой эпилепсией

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Резюме

Введение: Нет надёжных проспективных исследований эффективности леветирацетама (ЛЕВ) среди взрослых пациентов с лекарственно-устойчивой эпилепсией из Болгарии.

Цель: Исследование было направлено на проведение открытого проспективного исследования различных аспектов эффективности леветирацетама (ЛЕВ) среди пациентов с лекарственно-устойчивой эпилепсией в Болгарии.

Материалы и методы: Исследование проводилось среди больных эпилепсией, выбранных из числа посетивших отделение неврологии Университетской клиники «Св. Георгий», Пловдив, Болгария. Пациенты заполняли дневники с указанием частоты приступов, тяжести и побочных эффектов. Были регулярные документированные посещения через 3 или 6 месяцев в течение первого года лечения ЛЕВ и через 6 месяцев после этого с динамической оценкой частоты приступов, тяжести, побочных эффектов и данных ЭКГ.

Результаты: ЛЕВ был назначен в качестве дополнительной терапии 135 пациентам (86 мужчин, средний возраст 35 лет). Наблюдалось относительно небольшое и постоянное динамическое улучшение тяжести приступов, удовлетворительное снижение частоты приступов у 49.6% участников, постоянное среднее снижение частоты приступов (48-58%) с 6-ого до 36-ого месяцев лечения и высокий уровень ответа (53-60%) за тот же период. Новые типы приступов (очаговые с нарушением сознания с переходом / без перехода в двусторонние тонико-клонические приступы) возникли у 4 пациентов. Были нежелательные явления (головокружение, нарушение памяти, агрессия, скованность, неэпилептические припадки, депрессия, беспокойство, нарушения речи, зрительные галлюцинации, сонливость, слабость тазовых мышц, спутанность сознания, нарушения сна, потеря аппетита, нестабильная походка, выпадение волос, угревая сыпь, генерализованная сыпь) у 13.33% пациентов.

Заключение: Лечение ЛЕВ связано с: низким и постоянным улучшением тяжести приступов, хорошим и постоянным улучшением частоты приступов, вероятным ухудшением контроля над приступами, вероятным появлением новых типов припадков, хорошей безопасностью и переносимостью.

Ключевые слова

побочные эффекты, эффективность, эпилепсия, леветирацетам, переносимость
