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ORIGINAL ARTICLE

Objective and Subjective Assessment of the Effect of Levetiracetam on Daytime Sleepiness in Patients with Epilepsy

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Abstract

Background Levetiracetam (LEV) is a newer generation antiepileptic drug with unique anticonvulsive mechanism of action. It has been reported to cause daytime sleepiness in 4–15% of patients with epilepsy.

Methods We studied the effect of 2000 mg LEV monotherapy on daytime sleepiness over a 3-month period in patients with epilepsy. The subjective assessment of daytime sleepiness was made through Epworth sleepiness scale (ESS), and the objective assessment—through four naps MSLT. Both procedures were performed at baseline and after a 3-month period of LEV treatment. The dynamics in ESS score was measured as a shift from normal to excessive daytime sleepiness or vice versa. We studied two MSLT variables—mean sleep latency for all four naps and sleep stage. The dynamics in the mean sleep latency from baseline to the end of the third month of LEV treatment was also measured.

Results Twenty five patients participated in our study. The subjective and objective assessment of daytime sleepiness matched in only five of them. In none of the patients, ESS score was worsened after therapy. There was no statistically significant difference between the subjective assessment at baseline and after therapy ($p = 0.250$). There was no statistically significant difference between the objective assessment of daytime sleepiness at baseline and after therapy ($r = 0.13$). The patients with prolonged mean sleep latency reached a deeper sleep stage after therapy. The daytime sleepiness assessment correlated only with seizure frequency—patients with > 1 seizure a year had less variation in the degree of daytime sleepiness, i.e. more constant mean sleep latency.

Conclusion LEV 2000 mg/day does not worsen the subjective and the objective assessment of daytime sleepiness in patients with newly diagnosed or untreated epilepsy.

Keywords Levetiracetam · Epilepsy · Daytime sleepiness · Multiple sleep latency test · Epworth sleepiness scale

1 Introduction

Levetiracetam (LEV) is a newer generation antiepileptic drug with unique anticonvulsive mechanism of action—binding to ubiquitous administered SV2A protein in the presynaptic neuron terminals [1]. It also possesses a broad antiepileptic spectrum and optimal pharmacokinetics.

Sleep disorders and daytime sleepiness are common in patients with epilepsy [2–4]. The most typical antiepileptic drugs' side effect consists of disrupted sleep architecture and variation in the degree of daytime sleepiness [5]. Sleep disturbances are not reported as common LEV side effects [6]. LEV as mono- or polytherapy has been reported to cause daytime sleepiness in 4–15% of patients with epilepsy [7]. Daytime sleepiness is a more frequently associated side effect of the classical antiepileptic drugs (AEDs) [8]

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and newer generation AEDs are reported to be more sleep friendly [9].

In patients with epilepsy the frequency of sleep disturbances including daytime sleepiness, is greater due to side effects of AEDs, the impact of seizures, inter- and ictal epileptiform activity, occurring in daytime and over nocturnal sleep. The effect of epilepsy and sleep is reciprocal and it is controversial, whether the impaired sleep worsens seizure control, or the poor seizure control worsens sleep quality. Both poor sleep quality and unsatisfactory seizure control result in excessive daytime sleepiness. The effect of AEDs is deeply involved in this field of interaction. There is a fusion of their effects on seizures on one hand and the effects on sleep architecture and daytime sleepiness on the other. This difficult differentiation of these effects explains the need of more profound knowledge about their isolated effects on both—epilepsy, sleep and daytime sleepiness.

Only few studies evaluating the effect of LEV on daytime sleepiness have been reported [10–12]. Most of them share similar disadvantages: a small number of participants, a single LEV dose or a short period of drug administration, comparison between healthy volunteers and patients, polytherapy within the group of AEDs, short periods of observation, etc. No Bulgarian studies about the effects of LEV on daytime sleepiness in patients with epilepsy have been performed.

The purpose of our study is to make a subjective and objective assessment of the effects of 2000 mg LEV monotherapy over a 3-month period on daytime sleepiness in patients with epilepsy.

2 Materials and Methods

The study is open, prospective, with the participation of 29 patients with newly diagnosed epilepsy, untreated epilepsy or with ceased antiepileptic therapy for at least a 3-month period prior to study onset. They attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria after one or more seizures to be diagnosed or treated adequately.

All study procedures were performed after approval of the Local Ethics Commission at the Medical University, Plovdiv, Bulgaria. Every patient was introduced to the study design and signed an informed consent form before participation in all study procedures.

The following inclusion criteria were used: a signed informed consent form; patients with epilepsy (no matter of etiology or seizure type); newly diagnosed epilepsy, already diagnosed but untreated epilepsy or patients with ceased AEDs for at least a 3-month period prior to study onset; age between 18 and 75 years; patients untreated or undiagnosed with sleep disturbances; absence of other drug therapy affecting daytime sleepiness; absence of decompensated somatic illness; absence of poor sleep hygiene (night shifts occupation, alcohol abuse, psychotropic medications); absence of moderate to severe cognitive impairment. The diagnosis of epilepsy is in conformity with the ILAE criteria from 2014 [13].

Patients did not participate in the study if any of the following exclusion criteria was present: treatment with medications for other diseases affecting sleep and daytime sleepiness (beta blockers, antidepressants, H_1-blockers, opioid analgetics, etc.); patients treated with medications with direct effect on sleep and daytime sleepiness (hypnotics, benzodiazepines, barbiturates, neuroleptics, etc.); treatment with LEV for a period shorter than 3 months before the study onset; decompensated somatic diseases (cardio-vascular, renal, hepatic, hematologic, oncological, etc.); psychiatric and neurological diseases that could be associated with poor compliance; poor sleep hygiene—psychoactive medications, alcohol, narcotics or caffeine abuse, occupations affecting circadian rhythm sleep/wakefulness; moderate to severe cognitive impairment (according to MMSE result); pregnancy (no matter the term) and nursing; age under 18 and over 75 years; patients treated with another antiepileptic drug for a period shorter than 3 months before the study onset or during the study; no signed informed consent.

All participants underwent subjective, through Epworth sleepiness scale (ESS), and objective, through multiple sleep latency test (MSLT), assessment of daytime sleepiness at baseline and after a 3-month period of LEV 2000 mg treatment. All medical history, including epilepsy, was collected by a trained neurologist specialized in epilepsy through an examination of the patients' medical documentation and a detailed interview on the disease onset, heredity, concomitant diseases, type and etiology of epilepsy, seizure type, frequency and severity, treatment with AEDs. A detailed physical and neurological examination, electroencephalography (EEG) and a neuroimaging study (CT and/or MRT), as well as blood sampling (full blood count, biochemistry, measurement of serum LEV level following a 3-month LEV treatment to verify compliance) were performed.

ESS was first used in 1991 to evaluate self-reported daytime sleepiness. It includes eight questions presenting everyday situations in which patients must graduate the chance to doze: "0" no chance, "1" slight and "2" moderate and "3" high during the preceding week. The final score is a sum of the scores from all eight questions. A result ≥ 10 indicates excessive daytime sleepiness [14]. This scale was used in patients with epilepsy and healthy volunteers on LEV therapy [10–12]. In our study, the dynamics in ESS score was measured (at baseline and following a 3-month LEV treatment), not as an absolute numerical expression, but as a shift from one category to another—from normal to excessive daytime sleepiness or vice versa.

MSLT was introduced in clinical practice in 1977 by William C. Dement and Mary Carskadon [15]. It is a reliable diagnostic tool for drug induced daytime sleepiness. We performed MSLT according to all established recommendations [16]. There were 4 nap sessions divided by equal 2-h periods. The nap sessions took place at 9 a.m., 11 a.m., 1 p.m., and 3 p.m. MSLT was performed in sleep lab conditions and all patients kept their usual sleep regimen for at least 1 week before the study. Visual analysis was used by sleep medicine-certified physicians for scoring. Two variables of the study were evaluated: one quantitative—mean sleep latency for all four naps and one qualitative—sleep stage (if falling asleep was registered). The dynamics in mean sleep latency from baseline to the end of the third month of LEV treatment was also measured.

Descriptive statistics were used to analyze the frequency, mean and standard deviation for the demographic characteristics as well as for baseline and after therapy scores of ESS and MSLT. The qualitative variables were cross-tabulated to calculate percentages and SE. The difference between the groups defined by clinical characteristics was explored using Chi-square test and Mann–Whitney *U* test. Wilcoxon Signed Ranks Test was used to compare pretest–posttest scores of MSLT and ESS as well as the sleep stages at baseline and after therapy. The effect size (r) for Wilcoxon and Mann–Whitney test was calculated as: $r = z/(\sqrt{N})$, where z is the value of the test statistic and N is the number of observations or pairs. The interpretation of r is: small effect (0.10–0.3), moderate effect (0.30–0.5) and large effect ($r >= 0.5$). All statistical analyses were conducted using SPSS version 23. MS Excel 2016 was used for graphical representation of results. All statistical tests were conducted at a 5% significance level.

3 Results

Of the 29 patients included in the study 4 were excluded due to poor compliance. Most participants (80%) were between 18 and 50 years of age. The mean age of the participants was 35.2 ± 16.69 years. In all 25 patients, LEV blood levels were within referent limits.

The demographic and clinical characteristics of the study participants at the study onset are presented in Table 1.

The EEG characteristics of the study participants at the study onset and following a 3-month period with LEV treatment are presented in Table 2.

The actual ESS score at baseline and following a 3-month period with LEV therapy is shown in Table 3.

In none of the patients, the ESS score was worsened after therapy, 22 (88%) participants declared that after a 3-month period on therapy, there was no change and in the remaining

Table 1 Demographic and clinical characteristics of the study participants at the study onset

Demographic and clinical characteristic	*N* (*P%*)
Sex	
Female	17 (68%)
Male	8 (32%)
Age	
18–35 years	16 (64%)
36–50 years	4 (16%)
> 50 years	5 (20%)
Education	
High school	19 (76%)
College or university	6 (24%)
Age of epilepsy onset	
≤ 18 years	7 (28%)
> 18 years	18 (72%)
Epilepsy diagnosis	
Newly diagnosed	15 (60%)
Already diagnosed	10 (40%)
Epilepsy type	
Generalized	20 (80%)
Focal	2 (8%)
Generalized and focal	3 (12%)
Seizure type	
Generalized	18 (72%)
Focal	2 (8%)
Generalized and focal	5 (20%)
Seizure frequency	
< 1 seizure a year	10 (40%)
> 1 seizure a year	15 (60%)
Seizure severity	
Mild	6 (24%)
Severe	19 (76%)
Etiology	
Unknown	15 (60%)
Metabolic/structural	10 (40%)
Focal neurological symptoms	
Present	14 (56%)
Absent	11 (44%)
Neuroimaging	
Normal	13 (52%)
Unrelated to epilepsy findings	1 (4%)
Related to epilepsy findings	11 (44%)
Comorbidities*	
Present	5 (20%)
Arterial hypertension	4 (16%)
Hypothyroidism	1 (4%)
Absent	20 (80%)

N number of patients, *P (%)* percentage of patients

*Comorbidities: one patient had both comorbidities

Table 2 EEG characteristic of the study participants

EEG finding	At study onset *N* (*p*%)	Following a 3-month period with LEV treatment *N* (*P*%)
Background activity		
Normal	17 (68%)	21 (84%)
Depressed and disorganized	8 (32%)	4 (16%)
Pathological activity		
Focal slow wave	5 (20%)	2 (8%)
Focal epileptiform	9 (36%)	7 (28%)
Generalized epileptiform	2 (8%)	2 (8%)
None	9 (36%)	14 (56%)

N number of patients, *P (%)* percentage of patients

Table 3 ESS score at baseline and after a 3-month period with LEV therapy

N	Baseline ESS score	ESS score after a 3-month period with LEV therapy
1	4	5
2	3	5
3	1	1
4	10	7
5	5	4
6	10	9
7	10	17
8	3	5
9	4	2
10	6	3
11	6	4
12	8	5
13	2	2
14	10	10
15	2	1
16	6	5
17	9	7
18	4	4
19	6	7
20	11	7
21	5	3
22	12	10
23	3	4
24	9	9
25	14	15
Mean ± SD	6.52 ± 3.55	6.04 ± 3.96

N consecutive number of patients, *SD* standard deviation

3 (12%), the daytime sleepiness was improved. Therefore, there is no statistically significant difference between the subjective assessment at baseline and after LEV therapy ($p = 0.250$).

Figure 1 shows the comparison of the mean ESS score at baseline and following a 3-month period with LEV therapy.

The mean sleep latency for all four naps and the deepest sleep stage at baseline and following a 3-month period with LEV therapy are shown in Table 4.

In 10 (40%) study participants, the mean sleep latency was prolonged, in 13 (52%) it was shortened and in the remaining 2 (8%) patients—unchanged (those two patients actually did not fall asleep in both MSLT investigations).

Figure 2. shows the comparison of the mean sleep latency at baseline and following LEV therapy.

There is no statistically significant difference between the objective assessment (in mean sleep latency for all four naps) of daytime sleepiness at baseline and following a 3-month period of therapy ($z = -0.64$, $p = 0.523$, $r = 0.09$).

Figure 3 shows the comparison of the mean sleep latency of each of the four naps at baseline and after LEV therapy.

We searched for a correlation of the daytime sleepiness assessment with the demographic and clinical characteristics of patients. We observed an association of the dynamics in the mean sleep latency with the initial seizure frequency—patients with more than one seizure a year had smaller change in mean sleep latency (Median = 1.25, $U = 122.00$, $z = 2.608$, $p = 0.008$, $r = 0.52$), i.e. LEV affects less their mean sleep latency. We found a correlation between mean sleep latency and reached sleep stage—patients with prolonged mean sleep latency actually reached a deeper sleep stage (at baseline—rs = − 0.888, $p < 0.0001$ and after a 3-month period of LEV treatment)—rs = − 0.524, $p = 0.007$).

The subjective and objective assessment of daytime sleepiness matched in only five patients: two of them had no dynamics in ESS and MSLT results and all the three patients with improved daytime sleepiness as subjective assessment actually had prolonged mean sleep latency as an objective

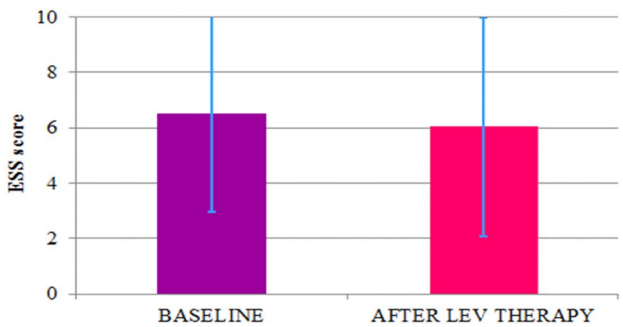


Fig. 1 Comparison of the mean ESS score at baseline and following a 3-month period with LEV therapy

Table 4 Mean sleep latency for all fournaps and the deepest sleep stage at baseline and following a 3-month period with LEV therapy

N	Baseline		Following a 3-month period with LEV therapy	
	Mean sleep latency for all four naps (min.)	Sleep stage	Mean sleep latency for all four naps (min.)	Sleep stage
1	7.75	N3	5.37	N2
2	8.00	N3	20.00	W
3	20.00	W	20.00	W
4	11.12	N3	16.00	N3
5	13.5	N1	15.75	N3
6	8.25	N3	16.25	N1
7	6.25	N3	7.50	N3
8	18.37	N1	12.87	N2
9	20.00	W	13.25	N2
10	15.87	N2	18.87	N1
11	8.75	N3	10.50	N2
12	20.00	W	16.25	N3
13	8.37	N2	2.12	N2
14	6.25	N3	5.62	N3
15	10.25	N2	4.25	N1
16	20.00	W	15.62	N1
17	18.5	N1	15.37	N2
18	10.62	N1	7.62	N2
19	3.75	N2	2.50	N2
20	12.25	N2	13.38	N2
21	11.88	N1	17.75	N1
22	20.00	W	20.00	W
23	14.50	N1	20.00	W
24	16.50	N1	13.50	N1
25	20.00	W	12.25	N1
Mean ± SD	13.23 ± 5.34	–	12.90 ± 5.73	–

N consecutive number of patients, *SD* standard deviation, *W* wake

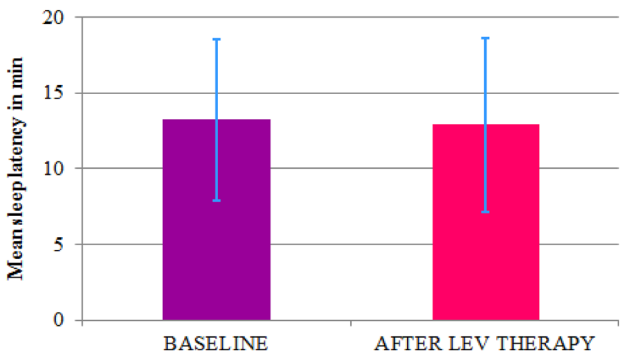
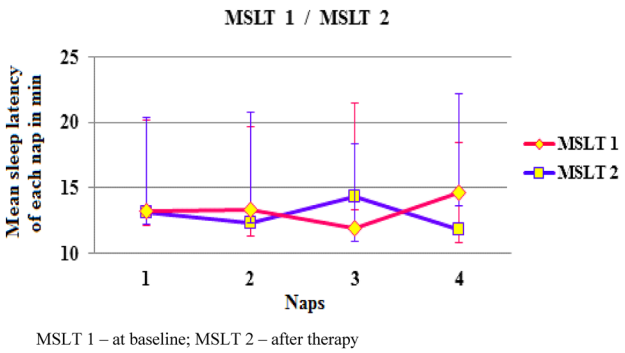


Fig. 2 Mean sleep latency in the study participants at baseline and following LEV therapy



MSLT 1 – at baseline; MSLT 2 – after therapy

Fig. 3 Comparison of the mean sleep latency of each nap at baseline (MSLT 1) and at the end of the 3-month with LEV therapy (MSLT 2)

assessment. In all the 13 participants with shortened mean sleep latency, the EES score did not show dynamics after therapy. Of the seven patients with prolonged mean sleep latency, in only three, the daytime sleepiness was improved according to the ESS results.

4 Discussion

The results from our study show that 2000 mg LEV therapy does not worsen either the subjective, or the objective assessment of daytime sleepiness in patients with newly diagnosed or untreated epilepsy.

These results are consistent with the data from a study with 14 healthy volunteers published by Cicolin et al. They were divided in two groups—on 2000 mg LEV and on placebo during 3-week period and after a wash out period they switched. On both regimes polysomnography, MLST and ESS were performed. The investigators did not find a statistically significant difference in the ESS score and the MSLT sleep latency between the placebo group and the group on treatment with 2000 mg LEV after 3 weeks of treatment [11]. Cho et al. also came to the conclusion that LEV did not affect the subjective assessment of daytime sleepiness using ESS and Pittsburg Sleep Quality Index (PSQI). The investigators applied ESS in 31patients with newly diagnosed focal epilepsy, 16 of them were treated with 1000 mg LEV and 15 with 400 mg Carbamazepine controlled release (CBZ-CR). Patients on LEV had increased wake after sleep onset and sleep efficiency, while patients on CBZ-CR had increased slow wave sleep, all other sleep parameters were unchanged in both groups. Their results showed that CBZ-CR affects sleep structure unlike LEV, which increased sleep efficiency without affecting sleep structure [10].

The results from the study of Yilmaz, however, confirmed a significant increase in both nap episodes and nap duration in 22 patients with focal epilepsy (LEV as add-on therapy) and 20 healthy volunteers after 3 weeks of 2000 mg LEV treatment. Only in the patients' group, sleep latency was shorter after LEV. All participants assessed subjective sleep quality with PSQI, daytime sleepiness with ESS and respectively with Maintainence of Wakefullness and wrist actimeter [12]. A possible explanation for the different results is the usage of another diagnostic tool (actimeter) for an assessment of daytime sleepiness and cumulative effects of two antiepileptic drugs.

Bell et al. monitored worsening of subjective daytime sleepiness in 13 healthy volunteers and 17 patients with epilepsy after a single dose of 1000 mg LEV. As a tool for measuring daytime sleepiness, they used St. Mary's Sleep Questionnaire (SMLQ) and Leeds Sleep Evaluation Questionnaire (LSEQ). In all 30 subjects, there were significantly different subjective LSEQ measures—the number of periods of wakefulness were fewer with LEV. In the volunteer group, there was no significant difference between SMQI results, however, in the patients group—the number of awakenings was reduced with LEV [17]. Our study was conducted using a different tool evaluating subjective daytime sleepiness—ESS. A possible cause for the difference in results could be the single dose of LEV avoiding accumulation of the drug and adaptive mechanisms against daytime sleepiness in chronic LEV use. Another possibility could be adding LEV to another antiepileptic drug (CBZ) in the patients' group resulting in potential additive effect on daytime sleepiness of the two drugs. For this reason in our study, the observation period was 3 months and LEV was used as monotherapy in a higher dose.

Zhou et al. also observed a significant increase in the ESS score after 3 weeks of LEV treatment compared to the baseline in ten patients with focal epilepsy, while in ten healthy volunteers, the ESS score remained unchanged. Regarding MSLT sleep latency, as in our study, no statistically significant difference was found after LEV therapy in both groups [18]. The smaller number of participants and the lower daily dose of LEV (1000 mg/day) could be associated with the difference from our study results.

Favorable key points in our study design are the longer period of observation allowing assessment of the chronic effects of LEV and the comparison of the results about objective and subjective daytime sleepiness only in patients with epilepsy at baseline and after a 3 months period. The comparison between healthy volunteers and patients with epilepsy unavoidably interposes the established negative impact of epilepsy and seizures on daytime sleepiness, likewise assessment only in healthy volunteers has the same pitfalls.

New results from our study, without analogue in literature, are the confirmed association of the dynamics in the mean sleep latency with the initial seizure frequency and the correlation between the prolonged mean sleep latency and the deeper sleep stage reached by patients. The latter suggests an independent effect of LEV on sleep depth, isolated from that on sleep latency.

5 Limitations

Our study has some limitations. The first one is the relatively small number of participants. The usage of appropriate statistical analyses however, assures the results reliability. Another limitation is the well-known interaction of epilepsy as clinical manifestations and epileptiform activity with nocturnal sleep and daytime sleepiness. It is hardly possible to distinguish the direct and indirect effects of LEV on epilepsy and daytime sleepiness. On the other hand, the investigation

of LEV effects on daytime sleepiness in healthy volunteers would not be relevant for patients with epilepsy. Future studies on the effects of LEV and other AEDs are needed to obtain more information on this topic.

6 Conclusion

Although daytime sleepiness is a commonly reported side effect of AED therapy, our results prove that LEV has no such a negative impact, which may contribute to its choice in the clinical practice. Our results suggest another important effect of LEV—facilitation of sleep depth. The abovementioned conclusions and the possible correlations of daytime sleepiness with various clinical characteristics would be an appropriate topic of future studies with a larger number of participants and parallel evaluations of other AEDs.

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Data availability The authors declare the availability of data associated with the study.

Declarations

Conflict of interest None.

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