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Effect of levetiracetam on nocturnal sleep in patients with epilepsy

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ABSTRACT

Aim of the study. The purpose of our study was the evaluation of the effect of 2,000 mg levetiracetam monotherapy over a 3-month period on nocturnal sleep in patients with epilepsy.

Clinical rationale for the study. Levetiracetam (LEV) is a novel antiepileptic drug with a unique anticonvulsive mechanism of action. It has been commonly reported to cause sleep disruption and daytime sleepiness in epilepsy patients. Its advantages (its broad antiepileptic spectrum, optimal pharmacokinetics, good safety and tolerability) have led to its frequent use in clinical practice, although little is yet known about LEV's effect on nocturnal sleep architecture.

Material and methods. The effect of LEV on nocturnal sleep was assessed through a full-night lab polysomnography (PSG), followed by a four-nap multiple sleep latency test. Both procedures were performed at baseline and after three months of LEV treatment. The dynamics of seven main PSG variables was evaluated prior to, and three months after, LEV therapy.

Results. Twenty five patients with newly diagnosed or untreated epilepsy completed the study. We found no statistically significant difference at baseline and after LEV therapy in the following sleep parameters: total sleep time, sleep onset, wake after sleep onset, N_1 stage and rapid eye movement (REM) sleep (minutes and percentages), and latency of all sleep stages including REM sleep. However, we found a statistically significant increase in the number of awakenings and arousals, an increase in N_2 and a decrease in N_3 stages (minutes and percentages) after therapy. We also observed an increase in N_1 stage and a trend toward a reduction in REM sleep (in both minutes and percentages), but they did not reach statistical significance.

Conclusions. Levetiracetam 2,000 mg/day does not affect sleep continuity and may be considered a sleep-friendly antiepileptic drug.

Key words: levetiracetam, epilepsy, nocturnal sleep, polysomnography

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Introduction

Sleep disorders and daytime sleepiness are common in patients with epilepsy [1–3] due to the side effects of antiseizure medications, the impact of seizures, and inter- and ictal epileptiform activity occurring during the day and during nocturnal sleep. The effects of epilepsy and sleep are reciprocal and it remains undetermined whether impaired sleep worsens seizure control, or whether poor seizure control worsens sleep quality. Both poor sleep quality and unsatisfactory seizure control result in excessive daytime sleepiness. On the other hand, it has been reported that sleep facilitates seizure activity in epilepsy [4]. Sleep electric activity is a powerful modulator of epileptic activity. Yet epileptic activity during sleep can alter the sleep/wake cycle and sleep structure [5]. Sleep-related problems represent a major comorbidity, and sleep architecture is significantly affected in patients with drug-resistant epilepsy [6].

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Epilepsy patients treated with levetiracetam (LEV) commonly complain of sleep disruption and daytime sleepiness [5, 7, 8]. Rarely reported side effects of LEV related to sleep include nightmares, somniloquy and confusion.

Only a few studies evaluating the effect of LEV on nocturnal sleep and sleep architecture have been reported [5, 9–12]. Most of them share similar disadvantages, such as: a small number of participants, a single or subtherapeutic anti-seizure medication dose or a short period of drug administration and observation, comparisons between healthy volunteers and patients, polytherapy within the group of anti-seizure medications. According to the published results, older generation anti-seizure medications typically reduce the percentage of rapid eye movement (REM) sleep and slow wave sleep, increase fragmentation, and induce daytime sleepiness [13–17]. According to the literature, LEV is associated with: 1. Reduction of REM sleep and waking after sleep onset (WASO), an increase in the duration of N_2 stage and improvement of sleep efficiency (SE) in both healthy volunteers and patients; 2. An increase in the total sleep time (TST) and the number of awakenings in healthy volunteers only; and 3. An increase in the duration of slow wave sleep in volunteers, but with the opposite effect in patients [6–11].

The aim of epilepsy therapy is freedom from seizures with the fewest possible adverse events and, preferably, monotherapy. In a retrospective study, Wężyk et al. [18] found predictors of remission in patients with epilepsy to be younger age, and shorter duration of epilepsy. They found that more frequently monotherapy and generalised epilepsies were associated with seizure freedom.

Levetiracetam is a new generation antiepileptic drug with a unique anticonvulsive mechanism of action in that it binds to ubiquitous administered SV2A protein in the presynaptic neuron terminals [19]. Its advantages (broad antiepileptic spectrum, optimal pharmacokinetics, good safety and tolerability) have led to its frequent use in clinical practice.

On the one hand, the ubiquitous distribution of SV2A in the brain in all presynaptic vesicles [20], and on the other hand its presence in vesicles using different neurotransmitters in both excitatory and inhibitory synapses, do not completely explain LEV's unique anticonvulsive effect. With that in mind, the effect of LEV on sleep architecture is also ambiguous: LEV modulates sleep by interfering with intrinsic sleep structure without altering sleep onset or duration. LEV facilitates particular sleep stages of NREM sleep and decreases REM sleep, but global sleep parameters such as sleep duration and efficiency remain unaffected.

Indications for LEV therapy are all types of seizures: focal, focal to bilateral tonic-clonic , and generalised tonic-clonic. It is prescribed as monotherapy in adults and adolescents with focal epilepsies and as add-on therapy in children and adults with focal and generalised epilepsies and it can be used in patients with absences, generalised and myoclonic seizures.

No Bulgarian study into the effects of anti-seizure medications on nocturnal sleep in patients with epilepsy has previously been performed.

The purpose of our study was the evaluation of the effect of 2,000 mg LEV monotherapy over a 3-month period on nocturnal sleep in patients with epilepsy.

Clinical rationale for the study

Since epilepsy patients commonly suffer from sleep disorders, which can be induced or worsened by therapy with anti-seizure medications, the widespread clinical use of LEV and the insufficient data on its effect on sleep architecture mean that there is a need for more profound investigations into this topic.

Material and methods

Our study was an open, prospective one in which 213 consecutive patients with epilepsy were screened in over a two-year period, although only 29 participated in the actual study and met all the inclusion criteria. The observation period was three months i.e. before the initiation of LEV therapy and up to the third month of treatment. The exact follow-up period was chosen to ignore possible confounding factors such as: transient acute effects of LEV and the resolution of potential adverse events on sleep and excessive daytime sleepiness after the initiation of LEV therapy. The follow-up was in fact the mean interictal period for most patients, which would have the effect of limiting the interaction of seizure impact on results. All 29 patients were newly diagnosed with epilepsy, or had untreated epilepsy, or had completed antiepileptic therapy of at least three-month duration prior to the study onset. They attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria after one or more seizures had been diagnosed or treated. The marketing authorisation holder and manufacturer of LEV was Actavis Group PTC ehf Iceland; film-coated 500 mg Noepix tablets were used in the titration period, and 1,000 mg tablets for the definite dosage.

All study procedures were performed after approval by the Local Ethics Committee at the Medical University, Plovdiv. Every patient understood the study design and gave written informed consent before participating in any study procedure.

We adopted the following inclusion criteria: a signed informed consent form; patients with epilepsy (regardless of aetiology or seizure type), or newly diagnosed epilepsy, or already diagnosed but untreated epilepsy, or patients who had ceased taking anti-seizure medications for at least three months prior to the study onset; age between 18 and 75 years; patients untreated or undiagnosed with sleep disorders including no subjective sleep difficulties; the absence of another drug therapy affecting daytime sleepiness; the absence of decompensated somatic illness; the absence of poor sleep hygiene; and the absence of moderate to severe cognitive impairment. Poor sleep hygiene was defined as working night shifts, alcohol,

psychoactive medication or caffeine abuse, and irregular bedtimes. All patients were screened with a specially designed questionnaire in order to exclude any of the abovementioned prior to study participation. The diagnosis of epilepsy conformed with the 2014 ILAE criteria [21]. Every patient had had two or more unprovoked seizures occurring > 24 h apart. The term 'newly diagnosed' denotes patients who had their second seizure confirming the diagnosis of 'epilepsy' immediately prior to study participation. Seizure and epilepsy types were categorised according to the 2017 ILAE classification [22, 23].

A complete medical history, including epilepsy, was collected by a trained neurologist who specialised in epilepsy by means of an examination of the patient's medical documentation plus a detailed interview regarding disease onset, heredity, concomitant diseases, type and aetiology of epilepsy, seizure type, seizure frequency and severity, and treatment with anti-seizure medications. A detailed physical and neurological examination, electroencephalography (EEG) and a neuroimaging study (computed tomography and/or magnetic resonance tomography), 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. All participants were given a seizure diary in which to record seizure frequency and severity, and a sleep diary in which to record sleep disturbances during the three months on LEV therapy.

All patients were on LEV monotherapy. The dose regime was uniform for all patients — 1,000 mg administered twice per day. The exact 2,000 mg daily dose was chosen as a mean therapeutic LEV monotherapy dose, and the titration period of a week was preferred mainly due to clinical considerations including seizure severity.

EEG was performed on a 16-channel SIGMA Medizin-Technik device using visual analysis on bipolar longitudinal montage twice: once at baseline and again following three months with LEV. Electroencephalography changes were evaluated both as background activity and as focal and generalised pathological epileptiform and/or non-epileptiform activity.

All patients underwent a full night sleep lab polysomnography (PSG) at baseline and again following three months of LEV treatment. We used 24 silver chloride electrodes, and all of the scalp electrodes (20 in number) were located according to the international 10–20 system. The number of scalp electrodes was comparable with the number of electrodes used in a standard EEG.

All hospitalised patients had a 2-day adaptation period before PSG recording, while outpatients sustained their usual sleep regimen for at least the same period. The beginning and the end of all PSG recordings complied with the individual preferences of the participant. All PSG procedures were performed at least 48 hours after the last epileptic seizure. PSG recording included electrooculography, electromyography, and electroencephalography. All PSG recordings were scored through visual analysis by trained and certified sleep medicine physicians according to the American Academy of Sleep Medicine criteria, version 2.4 updated in 2017.

The main PSG variables were:

1. Total sleep time (TST)
2. Sleep onset (SO)
3. Sleep efficiency (SE)
4. Wake after sleep onset (WASO)
5. Number of awakenings and arousals
6. N_1, N_2, N_3 stages and REM sleep latency
7. Time spent in N_1, N_2, N_3 stages and REM sleep in minutes and percentages of TST.

Following PSG, a four-nap multiple sleep latency test (MSLT) was performed for an objective assessment of daytime sleepiness. Each 20 min MSLT nap started at 9 a.m., 11 a.m., 1 p.m. and 3 p.m. PSG and MSLT were performed on a SomnoStar4 device using visual analysis on reference montage, each epoch was manually scored, and epileptiform/non-epileptiform EEG activity was analysed in addition to sleep stage.

Descriptive statistics were used for the demographic characteristics as well as for baseline and after therapy PSG sleep parameters. The qualitative variables were cross-tabulated to calculate percentages. A Wilcoxon Signed Rank Test was used to compare pre-test vs post-test scores of PSG parameters at baseline and after therapy. The effect size (r) for the Wilcoxon Signed Rank 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 ($r \geq 0.5$). McNemar's test was used to compare pre-test *vs.* post-test results of EEG and PSG background and pathological activity at baseline and after therapy. All statistical analyses were conducted using SPSS version 23. All statistical tests were conducted at a 5% significance level.

Results

Of the 29 patients included in the study, four (all males) were excluded due to poor compliance after the baseline PSG and MSLT. One patient discontinued the study because of a radical meningioma extirpation diagnosed after the study onset, but continued LEV therapy post-surgically. The other three excluded patients did not perform the second PSG and MSLT, but also continued LEV therapy. Most participants (80%) were between 18 and 50 years of age. The mean age of the participants was 35.20 ± 16.69 years. In all 25 patients who finished the study, compliance was good — the LEV blood levels after three months of therapy were within reference limits (10–40 mg/L; 22.52 ± 8.85). The therapeutic 2,000 mg LEV dose was titrated in a 1-week period and was well-tolerated. Only 11 patients reported transient mild to moderate side effects i.e. somnolence and/or dizziness. This resolved in double the titration period time and did not lead to discontinuation of LEV therapy. Data from sleep diaries did not reveal any

subjective dynamics in sleep routines except for 10 patients with adverse events consisting of somnolence and/or dizziness only in the first two weeks of LEV therapy. Only four patients had a seizure in the 3-month observation period, and none of them experienced any aggravation in seizure severity.

The demographic and clinical characteristics of the 25 participants at the study onset are set out in Table 1.

The majority of patients had generalised epilepsy (80%) and generalised seizures (72%). Interestingly, in all patients with focal and focal and generalised epilepsy, the neuroimaging study did not confirm a structural lesion, but a structural lesion was observed in 10 patients with generalised epilepsy.

Most patients presented with normal neuroimaging findings (52%), and only one patient had an abnormal finding unrelated to epilepsy i.e. parietal and cerebellar cortical atrophy. The other 10 (44%) patients' neuroimaging studies revealed lesions related to epilepsy i.e. had lesional epilepsy or structural aetiology as follows: 20% hippocampal asymmetry (but not sclerosis), 8% vascular encephalopathy, 8% encephalomalacic cyst, in one patient (4%) arteriovenous malformation, and in one patient (4%) periventricular leucomalacia.

In both EEG and PSG, the majority of patients presented with normal background activity — 68% for both studies prior to LEV therapy and 84% for EEG and 88% for PSG following a 3-month period with LEV. The dominant pathological finding in both studies was focal epileptiform activity: before LEV this was 36% in EEG and 52% in PSG, and after LEV therapy this was 28% and 48% respectively. In EEG prior to LEV, only 36% had no pathological activity; after therapy, this percentage increased to 56%. Similarly on PSG, before LEV, all patients had pathological activity, but after therapy it was absent in three patients.

No statistical significance was determined in EEG background (McNemar binomial exact test, $p = 0.125$), or in pathological activity (McNemar binomial exact test, $p = 0.125$) at baseline and after therapy. Also, statistical difference was not obtained in PSG background (McNemar binomial exact test, $p = 0.063$), or in pathological activity (McNemar binomial exact test, $p = 0.250$) at baseline and after therapy.

The PSG variables (median and range) of the study participants at the study onset and following a 3-month period with LEV treatment and statistical significance are set out in Table 2.

There were no statistically significant differences at study onset and following a 3-month period with LEV treatment in terms of TST, SO, WASO or SE. We found an increase in the number of awakenings and arousals in 19 patients, whereas five patients indicated a decrease and in one participant there was no change compared to the baseline. There was a statistically significant median increase in the number of awakening and arousals following a 3-month period with LEV treatment (median = 123) compared to the baseline (median = 72), $z = -2.215$; $p = 0.027$ with moderate effect size ($r = -0.31$) (Fig. 1A).

No statistically significant differences were detected in the latency of N_1, N_2, N_3 stages and REM sleep at baseline and following a 3-month period of LEV treatment. But there was a significant increase in N_2 sleep time ($p = 0.041$) and percentage ($p = 0.015$), and a decrease in N_3 sleep time ($p = 0.005$) and percentage ($p = 0.004$), following a 3-month

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

Demographic and clinical characteristic	N (%)
Sex	
Female	17 (68)
Male	8 (32)
Age	
18–35 years	16 (64)
36–50	4 (16)
> 50	5 (20)
Education	
High school	19 (76)
College or university	6 (24)
Age at epilepsy onset	
≤ 18 years	7 (28)
> 18 years	18 (72)
Epilepsy diagnosis	
Newly diagnosed	15 (60)
Already diagnosed	10 (40)
Epilepsy type	
Generalised	20 (80)
Focal	2 (8)
Generalised and focal	3 (12)
Seizure type	
Generalised	18 (72)
Focal	2 (8)
Generalised 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)
Aetiology	
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	20 (80)
Absent	5 (20)

*Comorbidities: arterial hypertension and hypothyroidism

Table 2. Summary of statistical results of polysomnographic parameters before and after levetiracetam therapy

Sleep parameters	At study onset Median (range)	Following a 3-month period with LEV treatment Median (range)	P-value
Total sleep time [min]	393 (132–574)	413.5 (287–487)	0.510
Sleep onset [min]	18.5 (2.5–74)	12 (3–86)	0.282
Wake after sleep onset [min]	52.5 (0–234)	50.5 (1–199.5)	0.798
Sleep efficiency (%)	85 (42–97)	83 (57–97)	0.423
Number of awakenings and arousals	72 (8–322)	123 (44–199)	**0.027**
Stage N_1 (%)	11 (1.7–38.7)	13.7 (4.9–58.5)	0.389
Stage N_2 (%)	52.4 (32–76.2)	57.5 (39.5–75)	**0.015**
Stage N_3 (%)	12.4 (3.4–31.1)	5.9 (0–25.2)	**0.004**
REM sleep (%)	19.5 (3.3-39.7)	15.4 (0.9–28.8)	0.196
Total time spent in N_1 [min]	40 (7.5–152)	50.5 (21.5–168)	0.282
Total time spent in N_2 [min]	200.5 (75–340.5)	214 (116.5–348.5)	**0.041**
Total time spent in N_3 [min]	55 (11–117)	21 (0–117.5)	**0.005**
Total time spent in REM sleep [min]	70.5 (13–176.5)	58.5 (2.5–127)	0.435
Stage N_1 latency [min]	18.5 (2.5–74)	12 (3–86)	0.282
Stage N_2 latency [min]	30.5 (6.5–130)	27 (9–186)	0.484
Stage N_3 latency [min]	56 (13.5–250.5)	56 (0–335)	0.427
REM sleep latency [min]	115 (6–398)	150 (62–304.5)	0.211

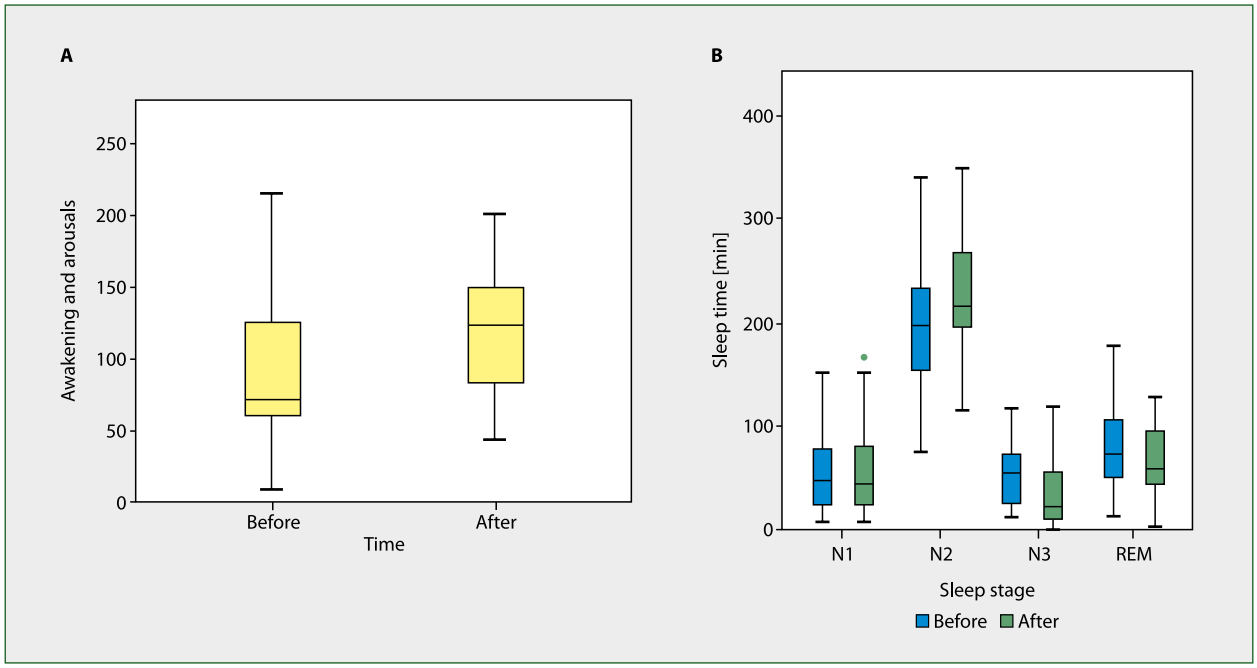

Figure 1. Number of arousals and awakenings (**A**) and time spent in N1, N2, N3 sleep stages (**B**) before and after LEV treatment

period of LEV treatment compared to the baseline (Fig. 1B). The effect sizes for N_2 and N_3 were moderate: r = –0.34 and r = –0.41, respectively.

We observed an increase in N_1 sleep time and percentage, and a trend toward a reduction in REM sleep time and percentage, but they did not reach statistical significance.

Table 3. Summary of studies' designs and results

Study disadvantages	Bell et al. [8]	Bazil et al. [12]	Cicolin et al. [5]	Yilmaz [10]	Cho et al. [9]	Zhou et al. [11]	Current study
1. LEV dose	1,000 mg	2,000 mg	2,000 mg	2,000 mg	1,000 mg	1,000 mg	2,000 mg
2. Duration of LEV therapy	Single dose	4 weeks	3 weeks	3 weeks	4–6 weeks	1 week	12 weeks
3. LEV therapy	Polytherapy LEV added to CBZ	Monotherapy	Monotherapy	Mono- or polytherapy to different anti-seizure medications	Monotherapy	Mono- or polytherapy to different anti-seizure medications	Monotherapy
4. Cohort	Healthy volunteers and patients with focal epilepsy	Healthy volunteers	Healthy volunteers	Healthy volunteers and patients with focal epilepsy	Patients with newly diagnosed focal epilepsy	Healthy volunteers and patients with focal epilepsy	Patients with epilepsy
5. Class of study	I	II	I	III	II	III	III
6. Number of subjects on LEV	28	16	14	52	31	20	25
7. Sleep features	→ TST, SL, awakenings ↑ N_2 ↓ N_4 patients only ↓ REM volunteers only	↑ awakenings with LEV → TST, SL, SE, REM latency, percentages of NREM and REM sleep	↑ TST, SE, N_2 and SWS ↓ REM sleep and WASO → SL and N_1	↓ total activity and SL ↑ nap episodes and duration → TST and SE	In LEV group ↓ WASO ↑ SE → TST, SL, REM latency, percentages of sleep stages, arousal index	In patients' group: ↓ REM sleep → TST, SL, SE, percentages and duration of NREM stages → SL от MSLT	↑ N_2 stage ↑ awakenings + arousals ↓ N3 stage → TST, SL, SE, percentages and duration of REM sleep and latency, latency of NREM sleep stages → SL от MSLT

↑ — increased; ↓ — decreased; → — unchanged; CBZ — carbamazepine; LEV — levetiracetam; MSLT — multiple sleep latency test; PSG — polysomnography; REM — rapid eye movement; SE — sleep efficiency; SL — sleep latency; SWS — slow wave sleep; TST — total sleep time; WASO — wake after sleep onset

There was no statistically significant difference between the objective assessment of daytime sleepiness, i.e. mean sleep latency for all four naps of MSLT, at baseline and after therapy.

Discussion

The results from our study show that 2,000 mg LEV monotherapy increased the time spent in N_2 stage, decreased the time spent in N_3 stage, and increased the number of awakenings and arousals i.e. induced sleep fragmentation in patients.

A summary of the design and results of all relevant studies is set out in Table 3.

All published studies which have focused on the effects of LEV on nocturnal sleep share common limitations: a small number of participants, which can result in unreliable conclusions; comparisons between healthy volunteers and epilepsy patients which do not take into consideration seizure impact or inter/ictal epileptiform activity; different LEV dose regimens and observation periods which possibly serves to mix up different acute and chronic effects of LEV on nocturnal sleep; and LEV as add-on therapy which may result in drug interactions and unreliable conclusions. The abovementioned disadvantages suggest contradictory and irreproducible conclusions of all studies.

Our study aimed to eliminate most of these disadvantages through the application of a stable therapeutic LEV dose, LEV monotherapy, a three-month observation period, and the inclusion only of epilepsy patients, so our obtained conclusions are more reliable. We used a uniform stable therapeutic LEV dose of 2,000 mg. LEV was applied as monotherapy in the absence of potential interactions or comparison with other anti-seizure medications. We chose a three months observation period to evaluate the effect of LEV over a longer period as a chronic therapy and at the same time potentially to distinguish its effect on sleep solely beside its effects on epilepsy, considering that only four patients had a seizure during the observation period. Therefore, the observational period was actually an interictal period for the majority of patients. We included only patients because we were aiming to focus on the effect of LEV on patients and avoid making a comparison between patients and controls and thereby ignoring epilepsy's impact on the results. For evaluation of the effect of LEV on

sleep architecture, a larger number of electrodes were applied, providing reliable comparability between pathological electrical activity from EEG and PSG. Though there was a certain heterogeneity in the clinical characteristics of our patients, the aim of our study was to assess the effect of LEV ignoring prior-to-therapy differences but in the presence and constancy of all these differences until the end of observation.

In conclusion, according to the results of all studies including ours, LEV changes sleep architecture in terms of changing the proportion of NREM sleep stages and REM sleep and potentiating sleep fragmentation. But all these interferences in the intrinsic sleep structure are proportional i.e. increase in N_2 stage and/or decrease in N_1, N_3 stages and REM sleep. Thus global parameters of sleep such as duration and efficiency remain unchanged.

In our study, the majority of patients had both generalised epilepsy and generalised seizures, which may influence the results. It is possible that LEV's effects on sleep architecture could be different in patients with focal epilepsy and focal seizure in as much as the distribution of epileptiform discharges is clinically and electrophysiologically different. Ten of the patients had structural aetiology of epilepsy which could affect sleep architecture according to the exact location of the lesion. On the other hand, all patients with focal structural lesions had generalised seizures. Moreover, the most common structural lesions are located in brain regions processing with acetylcholine as a neurotransmitter, which is the main neurotransmitter of REM sleep. As well as the mechanism of action of LEV affecting both excitatory and inhibitory synapses, it could also influence neurotransmission in divergent ways in structures involved in NREM and REM induction and maintenance.

Prior to study participation and during the observation period of three months, patients' comorbidities i.e. hypothyroidism (one patient) and arterial hypertension (four patients) both had optimal clinical and laboratory control with medications, i.e. normal blood pressure and a euthyroid state. All patients were on stable therapy for these comorbidities, which remained constant during the observation period, and therefore they were not confounding factors in our study.

Limitations

Our study has some limitations. The first is the relatively small number of participants. The use of appropriate statistical analyses however to some extent implies the results' reliability. Another limitation is the well-known interaction of epilepsy as clinical manifestations and epileptiform activity with nocturnal sleep. It is very difficult to distinguish the direct from the indirect effects of LEV on epilepsy and nocturnal sleep. The possible direct LEV effect in acute therapy could be different in those in chronic therapy. This may be due to reciprocal interactions between LEV and epilepsy on the one hand and between epilepsy and sleep on the other, as a result of LEV accumulation and synaptic reorganisation. An investigation of LEV's effects on nocturnal sleep only in healthy volunteers would not be relevant for patients with epilepsy. Although it would be relevant to include a healthy control group cross-matching the patient group in our study, we did not include a control group due to ethical considerations.

Future studies on the effects of LEV and other anti-seizure medications on nocturnal sleep are needed to obtain more information on this topic.

Clinical implications

Our study results provide a sleep profile of LEV in this specific population i.e. patients with untreated, undiagnosed or with ceased anti-seizure medications therapy over a three months period. According to our results, LEV influences sleep architecture — the registered changes in the proportion of NREM sleep stages and increased sleep fragmentation, but these are not accompanied by changes in the sleep continuity — while making no changes to sleep onset, sleep efficiency or total sleep time. In our study, our emphasis was not only on the changes in sleep architecture per se, but on their interaction on sleep integrity as a continuum. Therefore, LEV may be considered a sleep-friendly anti-seizure medication.

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