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# The effect of levetiracetam monotherapy on subjective sleep quality and objective sleep parameters in patients with epilepsy: Compared with the effect of carbamazepine-CR monotherapy

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ABSTRACT

*Purpose:* There is relatively little known about the effects of new antiepileptic drugs (AEDs) on sleep. This study was done to evaluate the effect of levetiracetam (LEV) on subjective sleep quality and sleep architecture in patients with epilepsy, and the results were compared with the effects of carbamazepine-CR (CBZ-CR).

*Methods:* This is a longitudinal randomized controlled trial using two different treatments, LEV (1000 mg/day) or CBZ-CR (400 mg/day). Thirty-one subjects (16 LEV and 15 CBZ-CR) had partial epilepsy and were tested with an overnight polysomnography (PSG) with full 10–20 electrodes. Sleep questionnaires and National Hospital Seizure severity Scale (NHS3) were evaluated. PSG and the questionnaires were repeated after 4–6 weeks of treatment.

*Results:* In the LEV group, when treatment PSG findings were compared with baseline, there was a significant increase in sleep efficiency ($p = 0.039$) but no changes in subjective sleep parameters. In the CBZ-CR group, there was a significant increase in the percentage of slow wave sleep ($p = 0.038$) while other sleep parameters were not significantly changed after treatment. There were no significant differences in effects on sleep between the LEV and CBZ-CR groups.

*Conclusion:* LEV may increase sleep efficiency without major effects on sleep structure with an overall effect on sleep parameters comparable to CBZ-CR.



## 1. Introduction

Patients with epilepsy often suffer from inadequate or ineffective sleep.[1,2] Seizures themselves can disrupt sleep, even when they occur during wakefulness.[1] Impaired sleep can cause considerable impairment of daytime functioning and quality of life.[3–5] In patients with epilepsy, inadequate sleep can induce daytime drowsiness and memory dysfunction, and can also contribute to intractable seizures.[4] Prolonged impaired sleep may cause more severe seizures and intractability in some patients with epilepsy.[4,6]

Antiepileptic drugs (AEDs) have also been found to disrupt sleep and cause daytime drowsiness.[4,7–10] However, the effects of AEDs are variable and often difficult to distinguish from the effects of improved seizure control. Older generation AEDs typically reduce the percentage of rapid eye movement (REM) sleep and slow wave sleep (SWS), increase fragmentation, and induce daytime sleepiness except for carbamazepine that may increase SWS.[8,11–14] There is relatively little known about the effects of the new AEDs on sleep.

Levetiracetam (LEV) is a new generation AED used to treat both partial and generalized epilepsy. Its pharmacodynamics is not clearly known, but appears to be distinct from that of classic AEDs and unrelated to voltage-gated sodium channels, gamma-aminobutyric acid (GABA)- or glutamate-mediated synaptic transmission.[15,16] There have been few reports about the effects of LEV on sleep. A few studies have shown that LEV does affect some elements of subjective sleep perception in healthy volunteers and patients with partial epilepsy but has no affect on sleep structure in normal volunteers.[17–19]

This study was done to evaluate the effects of LEV on subjective sleep quality and sleep structures in patients with partial epilepsy, and the results were compared with the effect of carbamazepine-CR (CBZ-CR) in patients with partial epilepsy.

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## 2. Methods

The study was of a longitudinal randomized controlled trial using two different treatment regimens i.e., LEV (1000 mg/day) or CBZ-CR (400 mg/day). All participating patients were newly diagnosed partial epilepsy patients who had their first seizure between six and one month prior to entry into the study. Diagnoses of epilepsy and seizure type were based on history, clinical presentation, EEG or video-EEG monitoring findings, and neuroimaging. Patients with primary generalized epilepsy, as evidenced by EEG findings, were excluded. The study was approved by the Institutional Ethics Committee.

None of the patients had taken any other AEDs prior to the study. Patients with sleep problems were excluded from the study based on history, standard sleep questionnaires, screening for a stable sleep–wake routine, and overnight polysomnography (PSG). Subjects who had a seizure the day prior to- or during the PSG, excessive caffeine consumption (defined as more than 2 cups a day), alcohol abuse, illicit drugs, and psychoactive medications were excluded as well. The subjects did not report any significant change in their life style or routine daily activities during the study period. Thirty-six patients were enrolled of whom 5 were excluded due to poor compliance with medication or sleep studies, or they were lost to follow-up. Thirty-one patients completed the study (16 LEV and 15 CBZ-CR). Seven patients had temporal lobe-, 11 patients had frontal lobe-, and 5 patients had parietal lobe epilepsy. In 8 patients the seizure focus was unknown. The mean ages of LEV and CBZ-CR groups were $31 \pm 15.31$ and $29 \pm 9.31$, respectively. The dose for LEV was targeted at a maintenance dose of 1000 mg/day, and the dose for CBZ-CR was targeted at a maintenance dose of 400 mg/day. All subjects who remained on medication were able to tolerate the target dosages at least a month before their follow up sleep study. An overnight PSG using standard PSG electrodes including full 10–20 EEG electrode system, EMG, EOG, piezoelectrodes and nasal thermocouples (Grass Telefactor Technologies, RI, USA) was performed on each patient before and after treatment with each drug (weeks 4–6). Additionally, sleep questionnaires and National Hospital Seizure Severity Scale (NHS3)[20] were used each time after each PSG and we checked for any seizures or adverse events during follow-up visits. Sleep questionnaires were composed of sleep diaries, the Pittsburg Sleep Quality Index (PSQI),[21] the Korean version of the Epworth Sleepiness Scale (KESS),[22] Beck's depression inventory-2 (BDI-2) and the Hospital Anxiety Scale (HAS).[23] All PSG and questionnaires were repeated after 4–6 weeks of treatment. The PSGs were scored by a sleep technician using standard scoring procedures according to the 2007 edition of the AASM Manual for the Scoring of Sleep and Associated Events[24] and interpreted by a sleep medicine-certified physician who was blind to treatment. Variables studied in the PSGs included sleep latency, REM sleep latency, total sleep time, sleep efficiency, percentage of each sleep stage, arousal index, and Wake time After Sleep Onset (WASO). Sleep latency, sleep efficiency, and total sleep time were considered as the primary outcome measures and the rest of the objective parameters and all of the subjective parameters were considered as secondary outcome measures.

Using an $\alpha$ level of 0.05 and power of 80%, a sample size of 13 for each group was needed to detect a difference between groups. Assuming a dropout rate of 15%, a sample of at least 31 subjects was selected. Demographic data between two groups were compared by independent student's $t$-test and $x^2$-test. Repeated measures analysis of variance (ANOVA) test was performed on the change of sleep parameters from baseline. To compare the sleep effects of two groups at the same time, independent student's $t$-test was used. Differences were considered significant when $p$-value $< 0.05$. Statistical analysis was done on SPSS ver. 17.0.

## 3. Results

### 3.1. Clinical and demographic characteristics

Thirty-one patients with partial epilepsy completed the study (16 LEV, 15 CBZ-CR). The baseline PSG did not reveal any significant sleep disordered breathing, periodic limb movement of sleep, insomnia or sleep related movement disorders. There were no significant differences between the LEV and CBZ-CR groups with respect to age, sex, caffeine and alcohol consumption, BMI, and seizure frequency, nor were there any significant differences in sleep characteristics including sleep onset latency, sleep efficiency,

**Table 1**
Summary of the characteristics and sleep parameters of the LEV group and the CBZ group in baseline state.

| | LEV ($n = 16$) | CBZ ($n = 15$) | $p$ |
|---|---|---|---|
| Age (year) | 31.44 ± 15.31 (15–66) | 29.80 ± 9.31 (15–49) | 0.724 |
| Gender (men/women) | 11 (68.8%)/5 (31.3%) | 11 (73.3%)/4 (26.7%) | 0.779 |
| Caffeine (+) | 13 (81.3%) | 12 (80.0%) | 1.000 |
| Alcohol (+) | 3 (18.8%) | 7 (46.7%) | 0.135 |
| Smoking (+) | 5 (31.3%) | 5 (33.3%) | 1.000 |
| Exercise (+) | 4 (25.0%) | 3 (20.0%) | 1.000 |
| BMI | 22.82 ± 2.92 (17.8–26.6) | 22.25 ± 2.60 (17.7–27.6) | 0.436 |
| BDI-2 | 8.94 ± 5.62 (2–25) | 11.42 ± 5.71 (0–19) | 0.235 |
| HAS | 5.75 ± 2.54 (1–10) | 7.95 ± 3.15 (2–13) | 0.042 |
| NHS3 | 9.69 ± 4.42 (0–18) | 7.47 ± 4.31 (0– 13) | 0.168 |
| Sleep parameters | | | |
| PSQI | 4.69 ± 3.28 (1–15) | 4.67 ± 1.84 (1–7) | 0.983 |
| KESS | 5.25 ± 4.27 (0–18) | 4.94 ± 2.80 (1–10) | 0.849 |
| Polysomnography | | | |
| Sleep latency | 12.25 ± 14.55 (0.5–58.0) | 13.93 ± 17.74 (0.5–66.0) | 0.774 |
| REM latency | 132.66 ± 68.37 (52–287.5) | 115.60 ± 75.38 (61–353.5) | 0.514 |
| Total sleep time | 383.36 ± 65.13 (200.5–477.9) | 395.83 ± 56.01 (266.5–459.6) | 0.573 |
| Sleep efficiency | 84.32 ± 13.65 (45.59–99.3) | 86.98 ± 11.54 (59.8–98.3) | 0.565 |
| Stage N1% | 9.92 ± 4.22 (3.10–19.5) | 10.39 ± 3.72 (4.60–18.9) | 0.743 |
| Stage N2% | 51.38 ± 8.34 (35–67.5) | 49.19 ± 7.44 (39.5–59.8) | 0.448 |
| Stage N3% | 19.94 ± 7.79 (9.80–40.3) | 21.29 ± 9.76 (8.2–47.1) | 0.674 |
| REM% | 18.74 ± 4.48 (13.1–25.9) | 19.15 ± 6.22 (3.7–25.8) | 0.837 |
| Arousal index | 7.09 ± 3.91 (2.9–16.3) | 8.49 ± 4.32 (4.3–18.2) | 0.351 |
| WASO | 55.61 ± 56.06 (2.5–218) | 37.97 ± 33.46 (7–111) | 0.300 |

NHS3, National Hospital Seizure Severity Scale; PSQI, Pittsburgh Sleep Quality Index; KESS, Korean version of Epworth Sleepiness Scale; HAS, Hospital Anxiety Scale; BDI-2, Beck Depression Inventory-2; WASO, Wake time After Sleep Onset.

**Table 2**
Comparison of the effects on sleep in the levetiracetam treatment group.

| Clinical and sleep parameters | Levetiracetam ($n = 16$) | | |
|---|---|---|---|
| | Baseline | After treatment | $p$ |
| NHS3 | 9.69 ± 4.42 | 1.25 ± 1.92 | 0.001 |
| Hospital Anxiety Scale | 5.75 ± 2.54 | 4.06 ± 3.15 | 0.005 |
| BDI-2 | 8.94 ± 5.62 | 6.94 ± 4.61 | 0.023 |
| PSQI | 4.69 ± 3.28 | 4.31 ± 1.99 | 1.000 |
| KESS | 5.25 ± 4.27 | 4.38 ± 3.52 | 0.16 |
| Polysomnographic findings | | | |
| Total sleep time | 383.36 ± 65.13 | 409.96 ± 48.02 | 0.074 |
| Sleep latency | 12.25 ± 14.55 | 7.94 ± 10.84 | 0.099 |
| REM latency | 132.66 ± 68.37 | 128.09 ± 77.91 | 0.756 |
| Sleep efficiency | 84.32 ± 13.65 | 90.62 ± 4.77* | 0.039 |
| WASO | 55.61 ± 56.06 | 31.72 ± 38.88* | 0.047 |
| Stage N1% | 9.92 ± 4.22 | 9.41 ± 5.09 | 0.724 |
| Stage N2% | 51.38 ± 8.34 | 49.98 ± 7.70 | 0.540 |
| Stage N3% | 19.94 ± 7.79 | 22.31 ± 8.03 | 0.302 |
| Stage REM% | 18.74 ± 4.48 | 18.31 ± 4.07 | 0.763 |
| Arousal index | 7.09 ± 3.91 | 6.99 ± 5.14 | 0.717 |

NHS3, National Hospital Seizure Severity Scale; BDI-2, Beck Depression Inventory-2; PSQI, Pittsburgh Sleep Quality Index; KESS, Korean version of Epworth Sleepiness Scale; WASO, Wake time After Sleep Onset.
* Significant difference within the group ($p < 0.05$).

and total sleep time at baseline. However, comparing the differences in seizure severity using the NHS3 between baseline and treatment revealed a significant improvement in both groups ($p = 0.001$). After treatment in both groups, the HAS and BDI-2 showed a significant improvement ($p < 0.05$) (Table 1).

### 3.2. Subjective measures

Analysis of the sleep questionnaires showed no significant difference between baseline and post-treatment between the two groups, although there was a trend for a decrease in PSQI with CBZ (Tables 2 and 3).

### 3.3. Objective measures

In the LEV group, when post-treatment PSG findings were compared with baseline, there was a significant increase in decrease in the WASO ($p = 0.047$) and sleep efficiency ($p = 0.039$) (Table 2 and Fig. 1). However, there were no significant differences in total sleep time, sleep latency, REM latency, or percentages of sleep stages. In the CBZ-CR group, there were significant increases in the percentage of slow wave sleep ($p = 0.038$) while other sleep parameters were not significantly changed after treatment (Table 3).

**Table 3**
Comparison of the effects on sleep in the carbamazepine-CR treatment group.

| Clinical and sleep parameters | Carbamazepine-CR ($n = 15$) | | |
|---|---|---|---|
| | Baseline | After treatment | $p$ |
| NHS3 | 7.47 ± 4.31 | 1.07 ± 2.55 | 0.001 |
| Hospital Anxiety Scale | 7.95 ± 3.15 | 5.35 ± 3.56 | 0.002 |
| Beck Depression Inventory-2 | 11.42 ± 5.71 | 9.45 ± 4.81 | 0.037 |
| PSQI | 4.67 ± 1.84 | 3.80 ± 1.94 | 0.077 |
| KESS | 4.94 ± 2.80 | 5.67 ± 4.55 | 0.362 |
| Polysomnographic findings | | | |
| Total sleep time | 395.83 ± 56.01 | 410.85 ± 38.32 | 0.331 |
| Sleep latency | 13.93 ± 17.74 | 9.87 ± 10.20 | 0.733 |
| REM latency | 115.60 ± 75.38 | 93.23 ± 53.20 | 0.233 |
| Sleep efficiency | 86.98 ± 11.54 | 89.29 ± 7.10 | 0.46 |
| WASO | 37.97 ± 33.46 | 29.43 ± 27.15 | 0.061 |
| Stage N1% | 10.39 ± 3.72 | 9.42 ± 4.92 | 0.191 |
| Stage N2% | 49.19 ± 7.44 | 44.81 ± 8.66 | 0.074 |
| Stage N3% | 21.29 ± 9.76 | 26.78 ± 9.47* | 0.038 |
| Stage REM% | 19.15 ± 6.22 | 18.99 ± 3.81 | 0.394 |
| Arousal index | 8.49 ± 4.32 | 8.56 ± 4.93 | 0.842 |

NHS3, National Hospital Seizure Severity Scale; PSQI, Pittsburgh Sleep Quality Index; KESS, Korean version of Epworth Sleepiness Scale; WASO, Wake time After Sleep Onset.
* Significant difference within the group ($p < 0.05$).

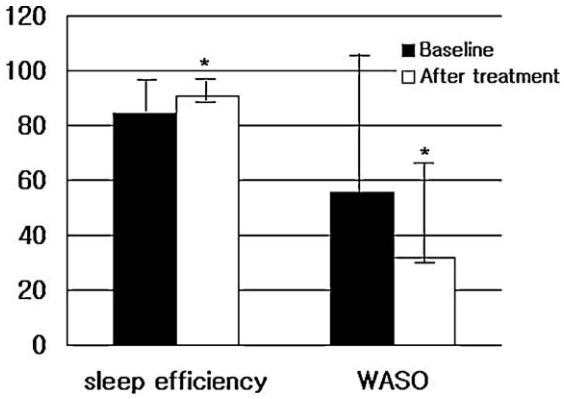


**Fig. 1.** Effects of levetiracetam on sleep efficiency. *Significant difference within baseline and after treatment ($p < 0.05$).

The overall effect on seizure reduction and sleep parameters of LEV was comparable to CBZ-CR, although there were some differences in the effects on individuals.

## 4. Discussion

These results suggest that in addition to its antiepileptic effects in patients with partial epilepsy, LEV stabilizes sleep and does not affect daytime sleepiness, as demonstrated by the significant increase in sleep efficiency, and no significant effect on subjective sleep parameters. Our results differ with some of the findings of the few available studies.[17,18] Bell et al.[17] have reported increased stage 2, decreased stage 4, and improved subjective sleep parameters with no change in objective measures of sleep continuity. These findings were seen in 17 patients with partial epilepsy treated with CBZ and LEV in a double-blind crossover placebo-controlled study compared to healthy controls. The same study also reported increased SWS, stage 2 sleep and REM latencies with CBZ. The fact that their patients were not treatment naive as in our study, as well as its crossover design might explain different results. The increase in the percentage of slow wave sleep in the CBZ group was similar to our finding. Bazil et al.[18] reported that LEV increased the number of awakenings with no other changes in any of the objective measures; however this study used only healthy volunteers.

Decrease in WASO was accompanied by improvement of sleep efficiency, although the percentage of NREM and REM sleep were unchanged. We considered the possibility that the decrease in WASO or increase in sleep efficiency could be due to seizure reduction, rather than a direct effect of LEV. Although the CBZ-CR group also had reduced seizure frequency, they did not share the same beneficial effects on sleep with the LEV group. Therefore, it may be presumed that LEV per se may increase sleep efficiency. The physiological mechanisms for these effects remain unknown. Although somnolence is known as a potential adverse effect of LEV,[25,26] our study showed that LEV did not increase daytime sleepiness throughout the KESS questionnaire in consistence with a prior report.[19] Therefore, further studies will be needed to clarify LEV's effect on sleepiness through objective measurements such as multiple sleep latency tests.

CBZ has been reported to improve sleep stability.[10] The effects of CBZ on sleep include improvement in sleep continuity, increase in total sleep time, decrease in REM sleep density, unchanged REM latency and percentage of REM sleep, and shortening of latency to sleep onset.[2,7,8,10] Our data showed that epilepsy patients on CBZ-

CR had an increase in SWS compared with the baseline phase consistent with previous published studies.[27] However, the effects of CBZ on REM sleep architecture were not observed in our study. Gigli et al. showed that REM sleep was reduced in patients with temporal lobe epilepsy and in seizure-free controls after acute administration of CBZ.[28] These effects were less pronounced after prolonged CBZ treatment.[8] Chronic CBZ-CR treatment did not significantly modify nocturnal sleep or daytime somnolence. Our study also shows similar results.

One limitation of our study might be the fact that the seizure focus in eight patients could not be confirmed by invasive recordings as it deemed clinically unnecessary. Also, the sleep studies were done in a sleep laboratory, which may have had some influence on the sleep quality. However, this is in consistence with the current standards of practice and there were no inter-subject variability in terms of study methods. Also, the dosages used in our patients were relatively low therapeutic doses and might not represent the effects of higher dosages. Further studies comparing different dosages might be needed to address this issue.

Despite significant individual differences in the effects of the two drugs, as for the two groups overall, the effects of LEV on sleep in patients with partial epilepsy were comparable to those of CBZ.

Many epilepsy patients have sleep disturbances which would have a negative effect on seizure control. Therefore, in choosing AEDs, one should consider the sleep effect of each AED.

## 5. Conclusion

These findings suggest that LEV may increase sleep efficiency without major effects on sleep structure or subjective sleep measures and an overall comparable effect to CBZ-CR.

## Conflicts of interest

None.

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