Igarashi T, Otani N, Yoshino A. Perampanel effects on sleep in epilepsy patients: A pilot case series on its therapeutic potential for sleep disorders. *Health Psychol Res*. 2025;13(4):e81240040.
https://doi.org/10.14440/hpr.0261

Research Article

Perampanel Effects on Sleep in Epilepsy Patients: A Pilot Case Series on Its Therapeutic Potential for Sleep Disorders

Takahiro Igarashi*, Naoki Otani, Atsuo Yoshino

Division of Neurosurgery, Department of Neurological Surgery, Nihon University School of Medicine, Tokyo 173-8610, Japan

(This article belongs to the *Special Issue: Connecting mind to body: the psychosomatic perspective*)

Keywords: α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid receptor, Epilepsy, Perampanel, Sleep disorders

Health Psychology Research

Vol. 13, 2025

Background

Sleep disorders are common among individuals with epilepsy, often leading to disturbances in sleep patterns and architecture. Certain anti-seizure medications adversely affect sleep independently of their anti-seizure effects.

Objective

This study aims to examine the impact of perampanel (PER) on sleep disorders in patients with epilepsy.

Methods

The effects of adjunctive PER therapy on circadian rhythm and daytime sleepiness were evaluated in epilepsy patients with comorbid sleep disorders. Twenty-one eligible patients were included, excluding those with liver failure or psychological disorders. This pilot case series assessed participants using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale. PER blood concentrations were measured. Patients were selected based on baseline PSQI scores ⩾6 (mean 11.57 ± 2.77).

Results

After 3 months of PER administration, the mean global PSQI score significantly improved to 6.71 ± 5.00 (p<0.01). Improvements were observed in PSQI components: C1 (sleep quality), C2 (sleep latency), and C6 (frequency of sleep medication use). A strong positive correlation was found between changes in PSQI scores (delta-PSQI = post-PER − pre-PER score) and PER blood concentrations (r = 0.71, p<0.01).

Conclusion

Adjunctive PER therapy significantly improved subjective sleep quality in epilepsy patients with comorbid sleep disorders. The correlation between the magnitude of improvements and PER blood concentration suggests a dose–response relationship. These findings indicate that PER may be a beneficial therapeutic option for managing sleep disturbances in this population and support the need for further investigation in larger, controlled studies.

1. INTRODUCTION

The relationship between epilepsy and sleep is intricate and bidirectional in nature. Epilepsy and certain therapeutic interventions have been associated with disturbances in sleep patterns and may contribute to the worsening of specific sleep disorders. Insomnia symptoms and sleep disorders are highly prevalent within the general population, affecting approximately 35–50% and 12–20% of individuals, respectively. These conditions may be attributed to coexisting medical or psychiatric disorders, pharmacological treatments, or substance use.[1] Insomnia can lead to inadequate management of epilepsy, and conversely, epilepsy may exacerbate insomnia. Multiple factors contribute to sleep disorders in individuals with epilepsy, such as poor sleep hygiene, comorbid sleep disorders, and circadian rhythm disturbances.[2] Seizures and interictal discharges have been shown to cause sleep fragmentation and alterations in sleep architecture.

***Corresponding author:**
Takahiro Igarashi
Division of Neurosurgery, Department of Neurological Surgery, Nihon University School of Medicine, Tokyo 173-8610, Japan
E-mail: igarashi.takahiro@nihon-u.ac.jp

Anti-seizure medications (ASMs) may influence sleep both positively and negatively, independently of their anticonvulsant properties.[3] Several studies have suggested that enhancing sleep hygiene and addressing sleep disorders may substantially improve clinical outcomes in individuals with epilepsy.[4] However, the etiology of sleep disturbances in this population is multifactorial, encompassing intrinsic features of epilepsy, seizure frequency, and the effects of ASMs. Patients with epilepsy may also experience various treatable sleep disorders, such as obstructive sleep apnea and periodic limb movements during sleep. These conditions contribute to sleep fragmentation and consequent excessive daytime sleepiness, which may adversely affect seizure control.

Perampanel (PER) has a distinct mechanism of action compared to other ASMs. PER is an approved medication for the treatment of epilepsy, acting as a non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) receptor, and can be used as a monotherapy or adjunctive therapy.[5] Somnolence is a common adverse effect of PER, and therefore, the medication is typically administered before bedtime.

This preliminary investigation examined the effects of PER therapy on sleep patterns and daytime somnolence in epilepsy patients with insomnia. In addition, it analyzed the correlation between sleep-related metrics and PER blood concentration.

2. MATERIALS AND METHODS

2.1. SUBJECTS

Patients diagnosed with both sleep disorders (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and Text Revision) and epilepsy, who experienced epileptic seizures more than once every 2–3 months despite receiving the maximum tolerated doses of ASMs for a minimum of 3 months, were recommended to initiate PER treatment based on clinical judgment. Patients with high-grade gliomas (World Health Organization [WHO] grades 3–4) were excluded from the study.

During the 3-month observation period, all patients underwent routine clinical and radiological follow-up, and no cases of tumor recurrence or regrowth were identified. Neuroimaging data were systematically reviewed to identify the location of residual lesions; none were found in brain regions directly involved in sleep–wake regulation, including the midbrain, thalamus, hypothalamus, or brainstem.

Patients were excluded if they had experienced a generalized tonic–clonic seizure within 72 h before enrollment, had impaired verbal or written communication, liver failure, or psychiatric disorders other than sleep disorders. Patients who agreed to participate completed the questionnaires while in the dispensary. Demographic and clinical data were collected by the attending doctor and extracted from medical records.

Concomitant medication use was systematically evaluated at enrollment and throughout the study. In addition to ASMs and sleep medicines specified in the study, no patients received psychotropic agents, stimulants, or other pharmacological treatments known to affect sleep or wakefulness. Moreover, none had recently discontinued such medications before enrollment. Medication regimens remained unchanged throughout the study to avoid alterations in drug pharmacokinetics or confounding of the sleep-related outcomes.

This study was conducted as a preliminary clinical investigation involving a cohort of 21 patients. Due to its exploratory nature and limited sample size, a placebo comparator group was not included. The primary aim was to gather pilot data on safety and preliminary efficacy rather than to establish definitive clinical outcomes. Findings are intended to inform future randomized controlled trials with larger sample sizes and more rigorous methodology.

2.2. SELF-REPORT QUESTIONNAIRE

Before PER initiation, patients' sleep quality and daytime sleepiness were evaluated using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI is a self-reported questionnaire comprising nine categories and ten subcomponents, each scored on a four-point Likert scale from 0 (absence of symptom) to 3 (symptom occurring 3 or more times per week), yielding a maximum score of 21. A PSQI score ⩾6 is indicative of a sleep disorder.[6] The ESS is an eight-item self-reported scale that evaluates daytime somnolence, with each item scored on a four-point scale from 0 (never dozed) to 3 (high frequency of dozing), yielding a maximum score of 24. An ESS score ⩾11 indicates excessive daytime sleepiness.[7]

2.3. MONITORING OF REST/ACTIVITY CYCLES

Actigraphy was conducted using a wristwatch-like actigraph (Micro Mini, A.M.I., United States of America [USA]) worn on the non-dominant wrist to continuously monitor three-dimensional movement. Standardized guidelines were used to identify anomalies, determine time in bed (TIB), and extract pertinent information. Actigraphy data were processed using designated analytical software (Action W-2, A.M.I., USA). As previously described, clinicians assessed total sleep time (TST), sleep efficiency (SE; calculated as TST/TIB × 100), sleep latency (SL), and nighttime wake duration.

2.4. FOLLOW-UP

Three months after PER initiation, patients who maintained a consistent PER dose and ASM regimen underwent blood testing and follow-up evaluation using the same sleep assessments as at baseline. PER blood concentrations were determined using standard pharmacokinetic procedures. Whole blood samples were collected and immediately centrifuged to separate plasma from cellular components. The resulting plasma fraction was used for all subsequent PER measurements to avoid variability related to hematologic factors, such as anemia, and to ensure consistency and reliability in pharmacokinetic analysis.

2.5. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Statistics Software Version 21.0 (IBM, USA). Data were expressed as mean ± standard deviation for normally distributed variables and as median with interquartile range for non-normally distributed variables. The Wilcoxon signed-rank test was employed to assess changes in scores. $p<0.05$ was considered statistically significant.

2.6. ETHICAL CONSIDERATION

The study was approved by the Committee for Clinical Trials and Research on Humans, and the ethical committee of the hospital approved the study protocol (RK-200714-12). Before participation, all individuals provided written informed consent after receiving full disclosure of the study's objectives, assurance of anonymity, and their right to decline participation or withdraw at any time.

3. RESULTS

The baseline characteristics and clinical data of the enrolled patients are presented in Table 1. PER was administered at doses of 4 mg/day (n = 17), 6 mg/day (n = 3), and 8 mg/day (n = 1). Concomitant ASMs included levetiracetam (n = 16); carbamazepine, lacosamide, and phenytoin (n = 2 each); and lamotrigine and valproic acid (n = 1 each). After a 3-month treatment period, 16 patients (76.2%) experienced a decrease in seizure frequency, and ten of these patients achieved seizure freedom. No adverse events were reported during the study period.

At baseline, the mean global PSQI score was 11.57 ± 2.77, indicating the presence of sleep disorders in all patients. Baseline ESS scores were within the normal range. After 3 months of PER treatment, a significant reduction in all PSQI component scores was noted (Table 2). No patients demonstrated excessive daytime somnolence following treatment. Significant improvements in TST, SE, and SL were observed as measured by actigraphy. The improvement in SL was statistically significant (p<0.01; Table 2).

To further validate the change in PSQI scores and confirm the effect of PER on sleeping disorders, delta-PSQI was compared with PER blood concentration. A strong positive correlation was identified (r = 0.71, p<0.01; Figure 1A). In contrast, no correlation was observed between post-treatment ESS scores and PER blood concentration (r = 0.15, p>0.05; Figure 1B).

4. DISCUSSION

The present study demonstrated that PER was effective and well-tolerated in the management of insomnia in patients with epilepsy, both when used alone and in combination with other therapies. PER administration resulted in reductions in sleep disturbances and improvements in specific sleep parameters, particularly sleep quality, SL, and the frequency of sleep medication use.

4.1. SLEEP DISORDERS IN PATIENTS WITH EPILEPSY

The prevalence of sleep disorders varied across populations. Based on international classification criteria (International Classification of Sleep Disorders, Second Edition, or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision), sleep disorders occur in approximately 20–25% of healthy adults.[8] In contrast, sleep disorders are observed 2 to 3 times more frequently in individuals with epilepsy.[9] Insomnia has been reported in up to 52% of epilepsy patients, and excessive daytime sleepiness affects up to 70%.[10] During the COVID-19 pandemic lockdown in the USA, approximately 25% of patients with epilepsy reported an increase in seizure frequency; among contributing factors, disrupted sleep patterns were the most frequently reported, affecting 63% of these patients.[11]

All patients in the present study had been receiving benzodiazepines before enrollment. No patient initiated benzodiazepine therapy or had their dose adjusted for the purpose of improving sleep during the observation period.

Table 1. Patient demographics and clinical characteristics

Case	Age (years)	Sex	Diagnosis	Concomitant AEDs	PER dose (mg/day)	Sleep medications
1	59	Male	Brain tumor	LEV	4	BZP, CPZ, ZPM
2	59	Male	Stroke	LEV, PHT	4	ETZ
3	58	Female	Brain tumor	LTG	4	ZPM
4	42	Male	Brain tumor	LEV	6	ESZ
5	68	Male	Brain tumor	LEV	4	ESZ
6	42	Female	Brain tumor	LEV	4	ESZ
7	68	Female	Brain tumor	PHT	8	ETZ
8	62	Female	Brain tumor	LCM	4	ESZ
9	58	Male	Trauma	LEV	4	ESZ
10	72	Female	Congenital disease	LEV	4	ZPM
11	40	Male	Congenital disease	LEV, VPA	4	ZPM
12	50	Male	Stroke	LCM	4	CPZ
13	43	Male	Brain tumor	LEV	6	ESZ, Suvorexant
14	80	Male	Trauma	LEV	4	ESZ
15	56	Male	Stroke	CBZ	4	ESZ
16	76	Male	Stroke	LEV	4	ZPM
17	91	Female	Trauma	CBZ, LEV	4	ESZ, Suvorexant
18	74	Male	Brain tumor	LEV	4	ETZ
19	60	Female	Brain tumor	LEV	4	ESZ
20	51	Male	Brain tumor	LEV	6	CPZ
21	63	Female	Trauma	LEV	4	ESZ

Abbreviations: AED: Anti-epileptic drug; BZP: Bromazepam; CBZ: Carbamazepine; CPZ: Chlorpromazine; ESZ: Eszopiclone; ETZ: Etizolam; LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; PER: Perampanel; PHT: Phenytoin; VPA: Valproic acid; ZPM: Zolpidem tartrate.

Table 2. Nighttime sleep and daytime sleepiness assessments before and after PER treatment (*n*=21)

Sleep assessment	Pre-PER (mean±SD)	Post-PER (mean±SD)	*p*-value
TST (min)	351.36±78.89	439.09±87.23	0.019*
SL (min)	51.43±30.54	23.18±18.20	0.008**
SE (%)	75.36±12.30	87.15±10.31	0.020*
Global PSQI score	11.57±2.77	6.71±5.00	0.002**
C1: Subjective sleep quality	2.00±0.32	1.00±0.89	0.001**
C2: Sleep latency	2.29±0.90	1.00±1.09	0.003**
C3: Sleep duration	1.57±1.03	0.95±1.20	0.029*
C4: Sleep efficiency	1.33±0.97	0.81±1.07	0.037*
C5: Sleep disturbances	1.05±0.38	0.90±0.30	0.068
C6: Sleep medication use	2.38±0.92	1.04±1.32	0.001**
C7: Daytime dysfunction	0.95±0.80	1.00±0.89	0.423
ESS score	3.95±2.87	4.52±2.93	0.028*

Notes: *p<0.05, **p<0.01.
Abbreviations: ESS: Epworth Sleepiness Scale; PER: Perampanel; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; SE: Sleep efficiency; SL: Sleep latency; TST: Total sleep time.

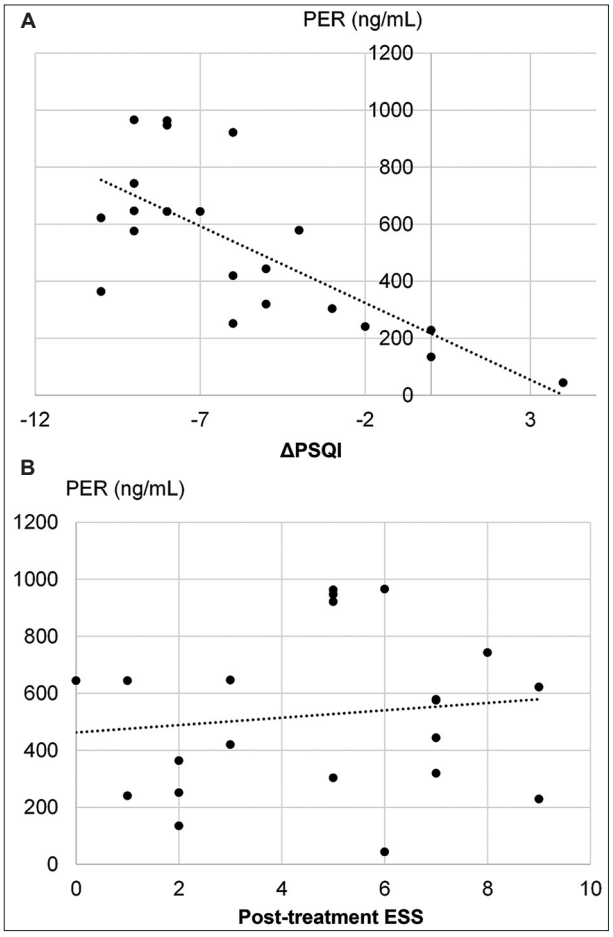

Figure 1. Relationship between perampanel (PER) blood concentration and Pittsburgh Sleep Quality Index (PSQI)/Epworth Sleepiness Scale (ESS) scores. (A) A significant positive correlation was observed between PER blood concentration and delta (Δ)-PSQI (r = 0.71, p<0.01). (B) No correlation was observed between PER blood concentration and post-treatment ESS score (r = 0.15, p>0.05).

This ensured that the effects of benzodiazepines on sleep remained stable, preventing potential confounding and allowing observed changes in sleep parameters to be attributed to PER.

Sleep disorders are also highly prevalent in drug-resistant epilepsy. Approximately 33% of individuals with medically refractory epilepsy experience obstructive sleep apnea.[12] Among patients with epilepsy referred for sleep evaluation, 5% had periodic limb movement disorder,[13] 18–35% had restless legs syndrome,[14] and 3.7% experienced central sleep apnea.[13] In our hospital, the prevalence of sleep disorders among patients diagnosed with epilepsy was 36%.

An additional factor that warrants consideration in this study was the potential influence of residual brain tumors on sleep regulation. Nearly half of the patients had a history of brain tumors; however, only low-grade gliomas or other non-high-grade lesions were included, and no patients with the WHO grade 3 or 4 gliomas were enrolled. There was no evidence of tumor recurrence or regrowth during the 3-month observation period. Neuroimaging confirmed that none of the participants had lesions involving brain regions responsible for sleep–wake regulation, such as the midbrain, thalamus, hypothalamus, or brainstem. Taken together, these findings suggest that tumor-related effects on sleep were unlikely to have influenced the results; however, this potential confounder should be considered in future studies involving patients with higher-grade or progressive lesions.

4.2. ASM EFFECTS ON SLEEP ARCHITECTURE

Previous research has examined the impact of ASMs on sleep patterns independent of seizure activity, demonstrating both beneficial and adverse outcomes.[15] Certain ASMs may alter sleep architecture and increase daytime somnolence, whereas others may help maintain stable sleep patterns.[16] Beneficial effects are characterized by the emergence of more consistent sleep cycles and reduced wakefulness during sleep in patients who respond to treatment.[17] Conversely, negative effects include disruptions in normal sleep cycle patterns.[18]

Recognition and appropriate management of sleep disorders in patients with epilepsy can improve seizure control, sleep quality, daytime functioning, and overall quality of life. Several studies have indicated that novel ASMs may exhibit beneficial impacts on the regulation of the sleep–wake cycle in contrast to traditional ASMs.[19] The findings of our study suggest that PER may play a role in enhancing therapeutic interventions for addressing sleep fragmentation.

Although the mean ESS score changed significantly following PER administration (pre-PER: 3.95 ± 2.87, post-PER: 4.52 ± 2.93; p=0.028), the absolute values remained well below the threshold for excessive daytime sleepiness, defined as an ESS score of 11 or higher. Consequently, no patient experienced clinically significant daytime sleepiness during the study period. This finding suggests that, while subtle changes in subjective sleepiness scores may occur, PER at the administered doses did not result in meaningful impairment of daytime alertness in our study.

4.3. GLUTAMATE AND SLEEP DISORDERS

Glutamate is the principal excitatory neurotransmitter in the central nervous system and a critical intermediary in cerebral metabolism. It plays an important role in the regulation of the sleep–wake cycle. Neurodegenerative disorders have been associated with impaired glutamate uptake, resulting in elevated neuronal death and sleep disturbances attributable to glutamate-induced excitotoxicity. Accordingly, glutamate transporters have been proposed as viable therapeutic targets for managing circadian rhythm sleep disorders in individuals with neurodegenerative conditions.[20] Comparable pathological mechanisms have been implicated in epilepsy. In the present study, 8 out of 21 patients (38.1%) exhibited sleep-cycle disorders.

Ahnaou *et al*.[21] reported that activation of glutamate receptors enhances wakefulness, diminishes deep sleep, and reduces functional network connectivity subsequent to the induction of slow alpha oscillatory activity. Additional studies have demonstrated the involvement of glutamate in sleep–wake regulation. A more recent investigation reported that sleep induces a net reduction in glutamate-containing AMPA receptors in the mouse motor cortex, both before and after learning.[22] In the present study, PER administration was associated with reductions in seizure frequency and improvements in sleep quality, suggesting a significant association between glutamate signaling, epilepsy, and sleep regulation.

4.4. AMPA RECEPTORS AND CIRCADIAN RHYTHM IN THE SUPRACHIASMATIC NUCLEUS (SCN)

The improvement in sleep observed with PER may be attributed, at least in part, to its modulatory effects on circadian rhythm regulation within the SCN. The SCN generates autonomous oscillations through clock gene transcription–translation feedback loops, which are entrained to the environmental light–dark cycle.[23]

Glutamate is a key neurotransmitter within the retinohypothalamic pathway.[24] Optic nerve stimulation has been shown to enhance glutamate release from retinohypothalamic terminals in the SCN.[25] In addition, the SCN expresses two ionotropic glutamate receptors: AMPA and *N*-methyl-*D*-aspartate receptors.[26] The phase-shifting effects of AMPA receptor activation have been extensively studied. Microinjection of AMPA into the mouse SCN induces phase shifts in circadian rhythms that mimic those produced by light exposure.[27] This study further demonstrated that AMPA-induced phase shifts occur in both behavioral rhythms and core clock oscillations. Importantly, these AMPA-induced phase delays were completely blocked by coadministration of 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide, a highly selective competitive antagonist of AMPA glutamate receptors, similar in action to PER.[27]

In our research, complete normalization of the sleep-wake cycle as observed in certain patients following PER therapy, suggesting that functional disruption of the SCN may have been present before the administration of PER.

4.5. EFFECT OF PER ON SLEEP QUALITY AND SOMNOLENCE

González *et al*.[28] reported that adjunctive low-dose PER therapy (4 mg/day) improved seizure control in individuals with epilepsy without impacting their sleep patterns or daytime somnolence. Their study did not demonstrate any effect of PER on SL, which may be attributable to the inclusion of patients with normal baseline sleep parameters (mean PSQI score: 4.10 ± 3.72; mean ESS score: 4.70 ± 3.65). In contrast, several studies investigating PER in epilepsy patients with sleep disturbances have reported a notable enhancement in sleep quality.[28-30]

In the present study, PER demonstrated beneficial effects on sleep quality, SL, and the frequency of sleep medication use. One possible explanation for this phenomenon is the rapid gastrointestinal absorption of PER. In a multi-dose study of patients with epilepsy, the time to maximum concentration ranged from 30 to 120 min.[31] Somnolence is a known adverse effect of PER; however, in patients with pre-existing insomnia, the sedative properties of PER may provide therapeutic benefit. Our findings suggest that PER exerts favorable sleep-modulating effects in this population.

4.6. LIMITATIONS

This study presents preliminary data on the effects of PER on sleep disorders in patients with epilepsy. Several limitations should be acknowledged:

(i) Sample size and placebo effects: The absence of a placebo-treated comparator group limits the ability to attribute observed effects solely to PER and increases the possibility of influence from placebo effects or natural variability in disease course. The relatively small number of participants (n = 21) further restricts the generalizability of the findings.

(ii) Pharmacokinetic interactions: Although concomitant drug effects are an inherent concern in clinical research, we verified that none of the participants were taking psychotropic agents, stimulants, or other medications known to alter sleep–wake regulation, nor did they have a recent history of such treatments before enrollment. This careful screening minimizes the likelihood that pharmacokinetic interactions confounded our results. However, the relatively small sample size limits the generalizability of our findings, and the possibility of subtle or undetected drug influences cannot be entirely excluded.

(iii) Nocturnal seizures: An important limitation of the present study is that sleep performance was assessed exclusively using actigraphy without concurrent electroencephalographic (EEG) monitoring. Although the enrolled patients had long-term seizure suppression and were not known to experience nocturnal seizures, subclinical events during sleep cannot be ruled out and may have influenced the observed improvements in sleep parameters. Consequently, the relative contributions of seizure control and the direct effects of PER on sleep cannot be fully disentangled. Future investigations incorporating continuous EEG or polysomnography will

be necessary to more accurately determine the specific impact of PER on sleep architecture independent of seizure activity.

These results should therefore be interpreted with caution and considered hypothesis-generating, with the ultimate goal of informing the design of future well-powered randomized controlled trials.

5. CONCLUSION

The current results indicate that PER may enhance seizure management while improving sleep quality and SL without inducing daytime somnolence.

ACKNOWLEDGMENTS

The authors acknowledge with respect the patients and their families who contributed to this study, and we are grateful to the outpatient nurses for their assistance in conducting the scoring assessments.

FUNDING

The present study was partially supported by Japan Society for the Promotion of Science KAKENHI (grant no. 24K12273).

CONFLICT OF INTEREST

Takahiro Igarashi and Prof. Atsuo Yoshino report personal fees and grants from Daiichi Sankyo, Eisai, and UCB Pharma. For the remaining authors, none were declared.

AUTHOR CONTRIBUTIONS

Conceptualization: Takahiro Igarashi
Formal analysis: Naoki Otani
Investigation: Takahiro Igarashi, Naoki Otani
Methodology: Takahiro Igarashi
Writing – original draft: Takahiro Igarashi
Writing – review & editing: Naoki Otani, Atsuo Yoshino

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Committee for Clinical Trials and Research on Humans, Nihon University School of Medicine (Approval ID: RK-200714-12). The ethical committee of the hospital also approved the study protocol (Approval No. RK-200714-12). Written informed consent was obtained from all participants for their participation in the study.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants for the publication of any data or images. All efforts were made to anonymize participants and conceal any identifying information in the text.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Submitted: 18 August 2025; Revision received: 27 September 2025; Accepted: 24 October 2025; Published: 14 November 2025

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