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ORIGINAL ARTICLE

Sleep–wake cycle and daytime sleepiness in patients with epilepsy after initiating perampanel as adjunctive therapy

Mariana Fernandes[1] · Clementina Lupo[1] · Matteo Spanetta[1] · Claudia De Masi[2,3] · Fabio Placidi[1,2,3] · Francesca Izzi[2,3] · Nicola Biagio Mercuri[1,4] · Claudio Liguori[1,2,3]

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Abstract

Background Antiseizure medications (ASMs) may affect nocturnal sleep and daytime vigilance. Perampanel (PER), a third-generation ASM, showed to improve nocturnal sleep in patients with epilepsy (PWE). Although ASMs can have beneficial effects on nocturnal sleep and daytime sleepiness, no study investigated the effect of PER on both sleep–wake cycle and daytime sleepiness. Therefore, this study aimed to objectively evaluate the sleep–wake cycle and daytime sleepiness in PWE treated with PER as adjunctive therapy.

Methods This prospective study included adult PWE who received PER as add-on treatment. Sleep–wake cycle was assessed through actigraphic monitoring and daytime sleepiness by the multiple sleep latency test (MSLT) performed at the end of the actigraphic recording. All patients performed both tests at baseline and at 6-month follow-up.

Results Ten patients (mean age: 44.50 ± 22.71 years, 50.0% female) were included. The mean monthly seizure frequency was 3.20 ± 5.94. Six of ten patients started PER as a first add-on treatment. The final PER dose was 5.11 ± 2.02 mg/day, and nine of ten patients achieved seizure freedom at follow-up. There was a significant decrease in mean monthly seizure frequency from baseline to follow-up ($p = 0.004$). No significant changes were found in the sleep–wake cycle parameters. An increase in sleep latency mean was observed at MSLT at 6-month follow-up ($p = 0.005$).

Conclusions This study confirms that adjunctive PER is effective on seizures without pathologically change of the sleep–wake cycle in PWE and can even improve daytime sleepiness. This effect can be mediated by the achievement of seizure control. Therefore, PER may be promising in PWE with sleep disturbances and daytime sleepiness.

Keywords Epileptic seizures · Anti-seizure medication · Sleep–wake · Somnolence · Actigraphy · Multiple sleep latency test

Introduction

The bidirectional relation between sleep and epilepsy is well established since disturbed sleep and sleep deprivation can trigger epileptic seizures, but also these latter can disrupt sleep [1]. Antiseizure medications (ASMs) used for treating epileptic seizures may also affect nocturnal sleep and daytime vigilance of patients with epilepsy (PWE). Specifically, ASMs may have a potential positive or negative impact on sleep architecture measured through polysomnography, on subjective sleep quality measured by questionnaires, as well as on daytime somnolence evaluated with the multiple wakefulness test (MWT) or multiple sleep latency test (MSLT) [2–4]. Recent studies have suggested that third-generation ASMs may have more beneficial effects on the sleep–wake cycle than the older ones [2–5]. Perampanel (PER) is a third-generation ASM and shows a significant beneficial effect on epileptic seizures since it acts on the modulation of glutamatergic post-synaptic transmission via non-competitive alpha-amino-3-hydroxy-5 methyl-4 isoxazolepropionic acid (AMPA) antagonism [6]. PER is approved as add-on treatment in patients with drug-resistant epilepsy, and its efficacy and tolerability have been widely documented, also when used as a first add-on treatment [7–12]. Among the newest ASMs, PER

✉ Claudio Liguori
dott.claudioliguori@yahoo.it

[1] Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy

[2] Sleep Medicine Centre, Neurology Unit, University Hospital of "Tor Vergata", Rome, Italy

[3] Epilepsy Centre, Sleep Medicine Centre, Neurology Unit, Neurology Unit, Department of Systems Medicine, University Hospital of Rome "Tor Vergata", Viale Oxford 81, 00133 Rome, Italy

[4] IRCCS Fondazione Santa Lucia, Rome, Italy

presents with a good profile on nocturnal sleep, measured by both polysomnography and validated questionnaires [13–16]. The mechanism of action of the drug can also explain its effect on sleep disorders, such as restless legs syndrome [17] or insomnia [18], thus reinforcing the clinical observation of its benefits on sleep in PWE. Considering that the most common adverse event of PER is daytime somnolence [19, 20], few reports tested the effects of PER on daytime vigilance and sleepiness, assessing these symptoms more through the use of subjective questionnaires than with objective tests [14–16]. Recent evidence described the dysregulation of the sleep–wake cycle in PWE [21], which can support both sleep impairment and daytime sleepiness of PWE. Actigraphy is a widely approved instrument to objectively monitor the sleep–wake cycle over a long period (from 1 week to 1 month, in general). Moreover, MSLT is recognized as the best instrument to monitor daytime sleep propensity and can help identifying central disorders of hypersomnolence. Therefore, in this study, the effect of PER on the sleep–wake cycle and daytime sleepiness was evaluated. In particular, objective instruments such as actigraphy and MSLT were performed in PWE at baseline and after 6 months of treatment by PER, which was used according to clinical practice and indication in PWE who showed persistent epileptic seizures although the prescription of an adequate ASM monotherapy or polytherapy.

Materials and methods

Participants and study design

PWE who started PER as an add-on treatment for better controlling their epileptic seizures were observed in this study. PER was prescribed and titrated in all patients according to clinical practice and guidelines at our epilepsy centre. Briefly, the initial titration of PER was 2 mg daily for 2 weeks, then followed by the increment to 4 to 10 mg daily until the follow-up visit [11]. Epileptic seizures and epileptic syndromes were classified according to the classification proposed by the International League Against Epilepsy — ILAE [22].

Eligibility criteria for the inclusion of patients in this study were (1) age ≥ 18 years old and (2) starting PER as adjunctive therapy for controlling epileptic seizures according to the regulatory approved indications. Exclusion criteria included (1) pregnancy or planned pregnancy, (2) planned surgery or surgery performed in the 2 months preceding the sleep studies, (3) history of suicide attempts, (4) history of drug or alcohol abuse, (5) diagnosis of neurologic or psychiatric disorders other than epilepsy, (6) shift work or jet lag, (7) sleep disorders (e.g. obstructive sleep apnea syndrome, restless leg syndrome) evaluated by a detailed medical interview and sleep medicine consultation, (8) ingestion of alcohol or caffeine on the day of the MSLT, and (9) occurrence of seizures during the 7-day actigraphic monitoring and in the 24-h before MSLT and checked by using the epilepsy diary. Specifically, subjects and/or their relatives were instructed to fill in a seizure log in order to obtain the baseline and follow-up seizure frequency. They were also instructed on the use of sleep logs and seizure diaries, which were filled in for the entire duration of the study.

At baseline, all patients underwent a clinical and neurological visit, including a sleep medicine interview, followed by a 7-day actigraphic recording coupled with sleep and seizure diaries, and in the morning after the last night of actigraphic recording a multiple sleep latency test (MSLT) was performed. At the end of these investigations, all patients started PER treatment (T0) and underwent a follow-up visit after 6 months of treatment (T1), according to the common clinical practice at our centre. At the follow-up visit, patients repeated the clinical and neurological visit, the 7-day actigraphic recording coupled with sleep and seizure diaries, and the MSLT.

For this study, the following data were collected from the clinical records of patients: adverse events, retention rate, PER dose, and monthly seizure frequency. The response rate for epilepsy was then evaluated as a reduction of ≥ 25%, ≥ 50%, and ≥ 75% than baseline (monthly evaluated before starting PER), or seizure freedom.

The study protocol was considered observational according to the STROBE statement by the internal review board of our institutional Ethical Committee. Written informed consent was obtained from all participants in the study.

Actigraphic recording

Actigraphy (Actiwatch2, Philips Respironics) was performed as previously described following the local guidelines of the sleep medicine centre owing to the same Neurology Unit [23, 24]. All patients started the monitoring at the end of the baseline visit before starting PER treatment and repeated it after the 6-month follow-up visit. Actigraphs were worn on participants' non-dominant wrist to gather activity and light exposure data for 7 consecutive days. Patients were instructed to push the button on the side of the watch at bedtime and wake time, as well as to follow their daily living routines. Patients also filled out a sleep diary before they went to bed each night and as soon as they woke in the morning.

Sleep and wake characteristics were separately monitored, and non-parametric circadian rhythm activity (NPCRA) was analysed with CamNTech MotionWare 1.2.26 by sleep medicine experts (CL, FI, FP) [23, 24]. The actigraphic parameters analysed were (see Table 1): time in bed (TIB), total elapsed time between the "lights off" and "got up" times; assumed sleep time (AST), sleep time excluding sleep latency;

Table 1 Description of actigraphic measure considered in the present study

Variable	Definition	Abbreviation
Quantitative actigraphic measures		
Time in bed	Time, in minutes, from bedtime to wake up time	TIB
Assumed sleep time	Time in bed after sleep latency	AST
Total sleep time	Sum of all epochs scored as sleep between sleep onset and wake up time, excluding sleep latency and wake periods	TST
Sleep latency	Interval, in minutes, between bedtime and sleep onset	SL
Sleep efficiency	Total sleep time divided by time in bed multiplied by 100	SE
Actual wake time	Sum, in minutes, of all epochs scored as wake between "fell asleep" and "got up" times	AWT
Central phase measure	Midpoint between "fell asleep" and "wake up," expressed as number of minutes past midnight	CPM
Total activity score	Sum of all activity counts during the assumed sleep period	TAS
Fragmentation index	Number of epochs with movement divided by TST duration plus number of consecutive epochs of immobility divided by the total number of immobility epochs multiplied by 100	FI
Day/night activity ratio	Daytime activity average/night time activity average	
Nonparametric actigraphic measures		
Interdaily stability	Ratio of activity level variance within each 24-h pattern to the overall activity level variance	IS
Intradaily variability	Ratio of the mean squares of the difference between consecutive hours and the mean squares around the overall mean	IV
M10	Average amplitudes of the most active 10-h period	M10
L5	Average amplitudes of the least active 5-h period	L5
Relative amplitude	Ratio of the most active 10-h period minus the least active 5-h period to the most active 10-h period plus the least active 5-h period	RA

total sleep time (TST), total time spent in sleep according to the epoch-by-epoch wake/sleep categorization excluding sleep latency and wake periods between "fell asleep" and "got up" times; sleep efficiency (SE), defined as the ratio between TST and TIB; sleep latency (SL), the time between "lights off" and "fell asleep"; central phase measure (CPM), the midpoint between "fell asleep" and "wake up," expressed as the number of minutes past midnight; actual wake time (AWT), defined as the duration expressed in minutes of "wake periods" between "fell asleep" and "got up" times; total activity score (TAS), defined as the total of all the activity counts during the AST ; fragmentation index (FI) defined as the sum of the "mobile time (%)" and the "immobile bouts < = 1 min (%)" and is an indicator of the degree of fragmentation of the sleep period; day/night activity ratio, expressed as daytime activity average/night time activity average. Regarding NPCRA, the following parameters were analysed: inter-daily stability (IS), quantifying the degree of regularity in the activity-rest pattern, with higher values corresponding to higher synchronisation; intra-daily variability (IV), quantifying the degree of fragmentation of activity rest periods, with higher values representing a very fragmented rest-activity rhythm; least 5 (L5) average activity, providing the average activity level for the sequence of the lowest five active hours; most 10 (M10) average activity, providing the average activity level for the sequence of the highest ten active hours; relative amplitude (RA), calculated by using the L5 to M10 measures and representing the synchronization with the average 24-h cycle, where higher values represent a better synchronized rest-activity rhythm [25, 26]. These parameters were obtained through the traditional analysis of circadian rhythms that fits physiological indicators to a Cosine waveform shape (Cosinor analysis) [27].

Multiple sleep latency test

The multiple sleep latency test (MSLT) was performed to objectively test daytime sleepiness. The test started the morning after the last night of actigraphic recording. Before starting the test, clinical researchers (CL, FP, FI) monitored that patient slept as usual during the actigraphic recording and showed a TST of the last night recorded longer than 6 h. Although polysomnography was not performed to confirm the total sleep time, researchers (CL, FI, FP) checked for the sleep habits of PWE also considering the sleep diaries. MSLT consisted of four trials performed at 2-h intervals and started 2 h after awakening [28, 29]. Daytime sleep measures were calculated for each participant, and the following parameters were collected: mean sleep latency (MSL) calculated as the average of the sleep latency in each trial of the MSLT; the number of sleep-onset REM

periods (SOREMPs), considered as the emergence of REM sleep during the sleep period in each session of the MSLT. According to the American Association of Sleep Medicine, a MSL of < 8 min was considered diagnostic of pathological sleepiness [30].

Statistical analysis

The statistical analysis was performed using commercial software SPSS version 25 [31]. The description of demographic and clinical data were reported as mean ± standard deviation or as counts and percentages. Response to treatment was described as absolute and relative frequencies. First, the Kolmogorov–Smirnov test was used to check the normal distribution of the data. The Wilcoxon signed-rank test was used to assess changes in clinical, MSLT, and actigraphic data between baseline and 6-month follow-up, and data were reported as medians and ranges. Effect sizes were calculated by Cohen's *d*, and the magnitude of the effects was interpreted with the following intervals: 0.1 to 0.3 small effect; 0.3 to 0.5 intermediate effect; 0.5 and higher strong effect.

Results

Ten patients with epilepsy (50.0% female), with a mean age of 44.50 ± 22.71 years old were included in the study. The mean illness duration was 14.20 ± 13.21 years. The majority of patients ($n = 6$; 60%) started PER as a first add-on treatment, while 20% ($n = 2$) started as a second and the other 20% ($n = 2$) as a third add-on therapy. The PER daily dose at follow-up was 5.11 ± 2.02 mg/day, and seizure freedom was achieved by 90% of patients. No adverse events and no drop-out were registered between baseline and follow-up. There was a significant decrease in median monthly seizure frequency from baseline (Md = 1.0) to 6-month follow-up (Md = 0) ($p = 0.004$, $d = 4.713$). The patient's demographic and clinical features at baseline and at 6-month follow-up are presented in Table 2.

Considering sleep–wake cycle data, as presented in Table 3, no significant changes were found from baseline to the 6-month follow-up in any of the sleep–wake and NPCRA parameters measured through actigraphy. At baseline, 1 patient showed pathological sleepiness (MSL = 7.125 min) and 2 had "borderline" values (both MSL = 8.50 min), while at the 6-month follow-up all patients showed normal MSL values. Consistently, a significant increase in the MSL at MSLT trials was observed at the 6-month follow-up (T0 Md = 12.81; T1 Md = 19.25; $p = 0.005$, $d = 3.842$). No SOREMPs were measured at baseline and follow-up in all patients. In Table 4, descriptions of MSLT data for each patient at baseline and follow-up were reported.

Table 2 Patients' demographic and clinical features at baseline and at 6-month follow-up

	Total ($n = 10$)
Female, *n* (%)	5(50.0)
Mean age	44.50 ± 22.71
Epilepsy mean duration in years	14.20 ± 13.21
Etiology, *n* (%)	
Genetic	1 (10.0)
Structural	3 (30.0)
Unknown	6 (60.0)
Seizure type, *n* (%)	
Generalized	3 (30.0)
Focal and Generalized	7 (70.0)
Lobe epilepsy	
Temporal epilepsy	5 (50.0)
Extratemporal epilepsy	5 (50.0)
Concomitant ASMs	
1 Concomitant, %	7 (70.0)
LEV	2
VPA	2
CBZ	1
LCM	1
PHB	1
2 Concomitants, %	
LCM	1 (10.0)
PHB	1
	1
3 Concomitants, %	2 (20.0)
ZNS	2
PHB	2
LCM	1
CBZ	1
Monthly mean seizure frequency at baseline (*n*)	3.20 ± 5.94*
Monthly mean seizure frequency at FU (*n*)	0.56 ± 1.67*
Seizure Frequency Rate at FU, *n*. (%)	9 (90%)
Seizure free	1(10%)
75% reduction	
Daily dose of Perampanel at FU (mg per day)	5.11 ± 2.03

Continuous data are presented as mean ± standard deviation

Abbreviations: ASM, antiseizure medication; *FU,* follow-up; *CBZ,* Carbamazepine; *LEV,* Levetiracetam; *LCM,* Lacosamide; *PHB,* phenobarbital; *VPA,* valproic Acid; *ZNS,* Zonisamide

*Significant changes between baseline and follow-up ($p = 0.004$)

Discussion

PER demonstrated its effectiveness and tolerability in PWE in real-world studies since reduced the frequency of epileptic seizures and also improves the burden of epilepsy-related comorbidities [7–12, 32]. Among all of the comorbidities, nocturnal sleep impairment and daytime sleepiness represent frequent complaints of PWE. Considering that ASMs can impact nocturnal sleep and daytime vigilance in PWE and that daytime somnolence is a common adverse event associated with PER, this study aimed to assess

Table 3 Actigraphy and multiple sleep latency test data at baseline and at the 6-month follow-up

	Baseline		6-month FU		Wilcoxon signed-rank		
	Median	Range	Median	Range	*Z*	*p*-value	***d***
Actigraphy data							
Time in bed (min)	539.50	330.85–639.29	522.93	417.86–632.71	−0.051	0.96	0.032
Assumed sleep time (min)	459.98	232.12–601.89	486.36	381.32–630.32	−0.663	0.51	0.429
Total sleep time (min)	422.81	184.71–530.36	424.59	349.14–601.36	−0.051	0.96	0.032
Actual wake time (min)	37.78	19.50–103.07	60.43	28.96–107.07	−0.968	0.33	0.643
Sleep efficiency (%)	77.72	56.67–93.42	82.21	75.88–95.00	−0.663	0.51	0.429
Sleep latency (min)	10.83	8.43–72.54	23.71	2.25–34.68	−1.478	0.14	1.057
Total activity score	3305.18	2450.17–9701.57	8220.00	2917.14–10,190.29	−1.172	0.24	0.798
Fragmentation Index	22.94	18.88–53.36	42.93	24.63–61.35	−0.968	0.33	0.643
Central Phase Measure (min)	173.92	46.59–320–02	245.21	139.46–382.25	-1.070	0.29	0.719
Day/night activity ratio	1.97	0.96–4.73	2.57	1.66–4.50	−0.764	0.45	0.497
NPCRA							
L5 Average	595.51	314.57–5460.54	1172.87	274.37–2848.90	−1.007	0.31	0.672
M10 Average	15,382.28	6017.16–24,087.89	14,114.86	8982.31–21,874.82	−1.070	0.29	0.719
Relative Amplitude (RA)	0.91	0.46–0.97	0.78	0–71–0.95	−1.274	0.20	0.880
Inter-daily Stability (IS)	0.64	0.39–0.78	0.49	0.46–0.79	−0.153	0.88	0.097
Intra-daily Variability (IV)	0.75	0.42–1.33	0.57	0.43–0.96	−0.357	0.72	0.227
MSLT							
MSL, min	12.81	7.13–18.25	19.25	12.00–20.00	−2.805	0.005	3.842

Abbreviations: *FU,* follow-up; *L5 Average,* least active 5 h average; *M10 Average,* most active 10 h average; *NPCRA,* non-parametric circadian rhythm analysis; *MSLT,* multiple sleep latency test; *MSL,* mean sleep latency

Table 4 MSLT data and ASMs for each patient at baseline and 6-month follow-up

	ASM	MSL at baseline	Add-on PER (dose at FU mg/day)	MSL at 6-month FU
Patient 1	LCM, ZNS, PHB	12.50	4	19.75
Patient 2	LCM	16.50	4	18.63
Patient 3	VPA	8.50	4	18.75
Patient 4	PHB	18.25	4	20.00
Patient 5	LCM, PHB	8.50	6	12.00
Patient 6	LEV	13.00	4	16.88
Patient 7	CBZ	12.63	4	13.88
Patient 8	LEV	7.125	6	20.00
Patient 9	VPA	16.50	4	20.00
Patient 10	PHB, CBZ, ZNS	18.00	10	20.00

Abbreviations: ASM, antiseizure medication; *FU,* follow-up; *MSL,* mean sleep latency; *CBZ,* Carbamazepine; *LEV,* Levetiracetam; *LCM,* Lacosamide; *PHB,* phenobarbital; *VPA,* valproic acid; *ZNS,* zonisamide

the effect of PER on the sleep–wake cycle and daytime sleepiness through the use of objective measures, namely actigraphy and MSLT. The actigraphic recording permitted the monitoring of the sleep–wake cycle for a long period without influencing the activities and the habits of daily living, also in PWE. In particular, it can measure nocturnal sleep and daytime motor activity, other than defining the sleep–wake rhythm. Therefore, the choice of actigraphy other than polysomnography, also preceding MSLT, although unconventional, was done to investigate a different clinical aspect of patients treated by PER.

The main finding of the present study was the reduced daytime sleep propensity measured by MSLT, based on the significant increase of the MSL after 6 months of add-on PER treatment in PWE. Moreover, the three patients presenting pathological or nearly pathological MSL at baseline, normalized the MSL at follow-up under adjunctive PER treatment. This improvement can be related to the significant reduction of epileptic seizures, which is also reflected by the achievement of seizure freedom in 9 of 10 patients at follow-up. Moreover, PER had no negative effects on the sleep–wake cycle, since the actigraphic data did not show a significant difference at follow-up. Previous studies demonstrated a positive effect of PER on sleep measured either subjectively or objectively; however, in agreement with our findings, the only study investigating the sleep–wake cycle in PWE treated by PER showed the lack of influence of the drug on the sleep–wake rhythm [13–16].

In the present study, the MSLT was performed at the end of the actigraphic recording in order to consecutively monitor nocturnal sleep and daytime motor activity of PWE and to evaluate the sleep–wake rhythm. Accordingly, actigraphy has been validated to study nocturnal sleep in PWE [33] since represents the best instrument to investigate the rest-activity rhythm in clinical and research contexts due to its economic and ecological characteristics [34]. Recently, actigraphy was used to monitor the 24-h rest-activity rhythm of PWE, and it was evident a sleep–wake pattern dysregulation in PWE compared to healthy controls, highlighting not only nocturnal sleep but also daytime activity impairment [21]. Moreover, MSLT was used to monitor daytime sleepiness since PER has been associated with daytime somnolence in PWE as a common side effect [19, 35]. MSLT has been widely demonstrated as a reliable objective test to study daytime sleepiness in PWE, although it was initially developed to assess daytime sleepiness only in hypersomnia syndromes [36]. Specifically, in the past decade, MSLT has been used in several studies evaluating the effects of different ASM on daytime sleepiness in PWE [37, 38].

Considering the results obtained by actigraphy, no effect of PER on nocturnal sleep and the sleep–wake cycle was evident. This result concords with previous literature showing that PER did not affect sleep quality or even improved certain sleep parameters, such as stage 3 of Non-REM sleep or sleep latency [13–16]. Consistently, Rocamora and colleagues documented an improvement in sleep architecture and subjective sleep quality in patients with focal refractory epilepsy without worsening subjective daytime sleepiness (measured with the Epworth Sleepiness Scale — ESS) after 12 weeks of adjunctive treatment with PER [14].

The novelty of the present study is the objective evaluation of daytime sleepiness in PWE treated with PER. Previous studies documented both positive or neutral effects of PER on subjective daytime sleepiness and objective daytime vigilance after PER treatment [13, 15, 16]. In the present study, PWE showed a significant increase in MSL, as a marker of reduced daytime sleep propensity, from baseline to the 6-month follow-up evaluation. The increase of the MSL at follow-up may be in contrast to the daytime sleepiness reported as a side effect in clinical trials [19, 20]. However, real-world studies documented a reduction in the frequency of adverse events due to PER treatment in PWE. This may be explained by the longer titration (from 2 to 4 weeks at 2 mg/day before increasing the daily dosage to 4 mg/day) and the lower dose of PER prescribed when it is used as first or second add-on treatment [11, 12]. Thus, the clinical practice may enable the reduction of adverse events promoting better tolerability of the drug. Another possible explanation for these data is the significant reduction of seizures in patients after starting PER treatment. Further studies should assess the potential beneficial role of seizure freedom on daytime sleepiness and vigilance in PWE treated by PER. Finally, in line with previous studies [7–9, 11, 12, 35], PER improved seizure control in our patients at the 6-month follow-up. In particular, adjunctive PER reduced the number of monthly seizures without significant modifications of the sleep–wake circadian rhythm. Due to the study design, our analysis did not allow establishing the reciprocal relations between seizures, the sleep–wake cycle, and the effect of PER. Nonetheless, it is possible to hypothesize that the beneficial effect of PER on sleep and daytime sleepiness may be not only related to the reduction of seizures but also related to the mechanism of action of the drug. In keeping with the PER pharmacodynamic profile, the effect on the glutamatergic neurotransmission may positively modulate the sleep–wake cycle, as previously reported in patients with RLS or insomnia [18, 39].

The present study has some limitations that need to be acknowledged. Firstly, the sample size is small and patients were not compared at baseline to a control group. Secondly, despite the 6-month follow-up that allowed a good estimation of the epileptic seizure control and the effect on sleep–wake rhythm and daytime sleepiness, future studies should consider the evaluation of the PER effects in a longer follow-up. Thirdly, subclinical seizures were not checked considering the absence of EEG recording before MSLT, although patients and their relatives were instructed to complete the seizure diary. Based on this preliminary observation, further studies evaluating the sleep–wake cycle should plan a protocol with polysomnography coupled with MSLT, and actigraphic recording, since it may allow monitoring subclinical seizures by the EEG signals. Fourthly, PER was prescribed as an add-on treatment in all patients according to clinical practice and guidelines, and the concomitant ASMs may also influence the sleep–wake cycle thus reducing the possible beneficial effect of PER. Finally, the presence of depressive or anxiety symptoms was assessed only during the neurological visit, and thus, subclinical psychiatric symptoms were not monitored by questionnaires and scales. Future studies should confirm this preliminary observation and explore the effects of PER on the sleep–wake rhythm and daytime somnolence in a larger group of patients distributing them according to the different concomitant ASMs and assessing depression and anxiety symptoms.

Conclusions

The findings of the present study suggest that adjunctive PER may improve both the control of seizures and improve daytime sleepiness by reducing daytime sleep propensity without affecting the sleep–wake cycle in PWE. Further studies with a larger sample should be carried out to identify the effects of PER and to increase the knowledge about its

beneficial role on nocturnal sleep, daytime sleepiness, and the sleep–wake cycle.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval The present study received the Ehitcal approval from the Independent Ethical Commettee of the University Hospital of Rome Tor Vergata (33/18).

Conflict interests CL served as a consultant for EISAI. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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