



Perampanel effects on seizures and sleep quality in people with epilepsy: A prospective multicenter study

G. Bergamo^a, M. Fernandes^a, S. Maio^b, G. Pauletto^c, A. Nilo^c, D. Arnaldi^d,
M. Puligheddu^e, L. Urso^f, F. Barbato^g, A. Cervellino^h, R. Renna^{i,j}, G. Boero^k,
Nicola Pilolli^k, A. Giordano^l, P. Penza^m, M. Lietoⁿ, M. Pezzellaⁱ, L. Giuliano^o,
M.P. Pasolini^p, M. Piccioli^q, I. Barbaro^b, L. Fernando^b, N.B. Mercuri^{a,b,*}, C. Liguori^{a,b,*}

^a Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

^b Neurology Unit, University Hospital of Rome Tor Vergata, Rome, Italy

^c Head-Neck and Neurosciences, Department, University Hospital of Udine, Udine, Italy

^d Department of Neurosciences, San Martino Hospital, Genoa, Italy

^e Sleep Study Center, AOU University Hospital of Cagliari, Cagliari, Italy

^f S. Antonio Abate Hospital Facility, Trapani, Italy

^g S. M. delle Grazie Hospital, Pozzuoli, Italy

^h Regional Hospital Authority San Carlo, Potenza, Italy

ⁱ Neurology – Stroke Unit, AORN Cardarelli, Naples, Italy

^j Department of Neurosciences, Neurology – Stroke Unit, AORN San Pio, Benevento, Italy

^k Division of Neurology, Ss Annunziata Hospital, Taranto, Italy

^l Department of Advanced Medical and Surgical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy

^m San Giovanni di Dio and Ruggi d'Aragona Hospital, Salerno, Italy

ⁿ Ospedale del Mare, Naples, Italy

^o Vittorio Emanuele University Hospital, Catania, Italy

^p Spedali Civili Hospital Authority, Brescia, Italy

^q San Filippo Neri Hospital, Rome, Italy

ARTICLE INFO

Keywords:

Antiseizure medication
Seizure
Insomnia
Daytime Sleepiness
Depression
Quality of Life
Circadian Sleep-Wake Cycle

ABSTRACT

Objective: Preliminary studies suggested a potential beneficial effect of perampanel (PER) on sleep in people with epilepsy (PwE). The present multicenter study evaluated the clinical potential of the early use of PER in PwE on seizures and on sleep quality, insomnia, daytime sleepiness and circadian rhythm preferences, as well as on depressive symptoms and quality of life.

Methods: PwE starting PER as early add-on antiseizure medication were evaluated at baseline (T0) and after six months of treatment (T1) using standardized questionnaires: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Morningness–Eveningness Questionnaire (MEQ), and the Quality of Life in Epilepsy Inventory (QoLIE-31).

Results: 74 PwE (44.6 % male, mean age 42.41 ± 18.06 years) were included and 59 PwE completed the study. At T1, 45.76 % (27/59) of PwE were seizure-free and significant reduction of seizures was found (10.80 ± 20.72 vs. 5.93 ± 16.77 , $p = 0.002$). At T1, a significant improvement in sleep quality (PSQI, 7.18 ± 4.27 vs. 4.63 ± 3.09 , $p = 0.001$) was evident, and particularly in sleep duration and efficiency and in the use of sleeping medications. Insomnia symptoms (ISI, 8.15 ± 6.23 vs. 5.32 ± 5.25 , $p = 0.002$) and quality of life (QoLIE-31, 58.32 ± 16.57 vs. 65.81 ± 16.31 , $p = 0.033$), mainly social functioning and perceived well-being, also significantly improved. No significant changes emerged for daytime sleepiness, circadian preference and depressive symptoms.

Discussion: These findings suggest that PER may represent a valid therapeutic option for PwE, and particularly in who presents sleep impairment and insomnia.

* Corresponding author at: Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy.

E-mail address: dott.claudioliguori@yahoo.it (C. Liguori).

<https://doi.org/10.1016/j.yebeh.2025.110748>

Received 13 August 2025; Received in revised form 26 September 2025; Accepted 27 September 2025

Available online 2 October 2025

1525-5050/© 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The bidirectional relationship between sleep and epilepsy is well known, whereby factors such as poor sleep and sleep deprivation can trigger epileptic seizures, whereas frequent seizures can disrupt sleep [1]. People with epilepsy (PwE) commonly report sleep problems, being insomnia the most frequent sleep disorder in this population [2]. Recent studies have demonstrated sleep-wake cycle impairment in PwE, highlighting the importance of monitoring the rhythm due to its association with seizure recurrence [3,4]. Sleep disturbances are concomitantly present with depressive symptoms, causing a vicious cycle between mood, sleep problems and seizures [5].

Moreover, antiseizure medications (ASMs) may affect sleep and behavior, and may contribute to daytime sleepiness [6]. Specifically, ASMs may have a potential positive or negative impact on sleep quality, daytime somnolence and depressive symptoms [7–9]. Recent studies suggested that the newest ASMs may have a more favourable effect on these patients' outcomes compared to older treatments [7–10].

Perampanel (PER), a third-generation ASM, is a selective, non-competitive antagonist of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, modulating glutamatergic postsynaptic transmission [11]. The effectiveness and tolerability of PER have been widely demonstrated in real-world studies both as first add-on treatment or in drug-resistant epilepsy [12–17], with somnolence being the most commonly reported adverse event in clinical trials [18,19]. Preliminary evidence from polysomnographic and subjective studies has shown that adjunctive PER may objectively improve sleep architecture and increase subjective sleep quality in people with focal refractory epilepsy [20,21]. However, the evidence remains limited regarding the early use of the drug, particularly at low doses (4–6 mg/day).

This real-world prospective multicentre study was primarily aimed at evaluating the effectiveness and tolerability of the early use of PER prescribed according to its approved indication and common clinical practice in PwE. Secondary aims of the present study were the evaluation of PER effect on sleep quality, daytime sleepiness, the sleep-wake cycle, and the psychological and functional well-being of PwE after six months of PER therapy.

2. Methods

2.1. Study design and participants

This was a prospective, multicentre, real-world observational study conducted over a 6-month follow-up period in adult PwE initiating PER as an early adjunctive treatment. PwE were enrolled at 16 different sites in Italy: University Hospital of Rome Tor Vergata; University Health Authority of Central Friuli, Udine; San Martino Hospital, Genoa; AOU University Hospital of Cagliari; S. Antonio Abate Hospital Facility, Trapani; S. M. delle Grazie Hospital, Pozzuoli; Regional Hospital Authority San Carlo, Potenza; Cardarelli Hospital, Naples; Santissima Annunziata Hospital, Taranto; Luigi Vanvitelli University Hospital Authority, Naples; San Giovanni di Dio and Ruggi d'Aragona Hospital, Salerno; Ospedale del Mare, Naples; Vittorio Emanuele University Hospital, Catania; Spedali Civili Hospital Authority, Brescia; San Filippo Neri Hospital, Roma. Eligible participants were adults (≥ 18 years of age) with a confirmed diagnosis of epilepsy according to the 2017 criteria of the International League Against Epilepsy (ILAE) [22]. PwE were required to be initiating PER as early add-on treatment for the persistent focal or generalized seizures although the previous pharmacological regimen, in accordance with current clinical guidelines and prescribing information.

Exclusion criteria included: known contraindications to PER use as per summary of product characteristics; ongoing pregnancy or planned pregnancy during the study period; scheduled surgery during the study or surgery performed within six months prior to baseline; history of suicide attempts or active suicidal ideation; diagnosis of non-epileptic

seizures; current or past diagnosis of substance (alcohol or drug) abuse.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Local Independent Ethics Committee with approval number R.S. 44.23 on March 10, 2023. All participants provided written informed consent prior to study inclusion.

Participants were evaluated at baseline (T0, prior to start PER treatment) and at the 6-month follow-up (T1). At both time points, a standardized clinical and neurological evaluation was conducted, and participants completed a battery of validated self-report questionnaires. Seizure frequency was recorded using seizure diaries maintained throughout the 6-month observational period. Demographic and clinical data, including seizure type, baseline seizure frequency (28-day average over the previous 3 months), concomitant ASMs, and detailed medical history, were collected from clinical records.

2.2. Measures

Participants completed a standardized battery of self-report instruments at both T0 and T1 to assess sleep quality, daytime sleepiness, circadian sleep-wake cycle preference, insomnia symptoms, depressive symptoms, and epilepsy-related quality of life.

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [23,24], a 19-item questionnaire that assesses subjective sleep quality and sleep disturbances over the previous month. It yields seven component scores—subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction—which are summed to obtain a global score ranging from 0 to 21. Higher scores indicate poorer sleep quality with a cut-off for defining poor sleep quality of 5.

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), an 8-item instrument that measures the likelihood of dozing off in common daytime situations [25,26]. Each item is scored from 0 to 3, with total scores ranging from 0 to 24. A total score of 10 or higher is generally considered indicative of excessive daytime sleepiness.

To assess the circadian preference of the sleep-wake cycle, the Morningness-Eveningness Questionnaire (MEQ) was administered [27,28]. This 19-item instrument evaluates individual differences in preferred timing for sleep and activity, classifying respondents into morning, intermediate, or evening chronotypes. Higher total scores reflect a stronger morning preference.

The Insomnia Severity Index (ISI) was used to assess the nature, severity, and impact of insomnia symptoms [29,30]. This 7-item scale uses a 5-point Likert response format (0–4), yielding total scores from 0 to 28. The total score is interpreted as follows: absence of insomnia (0–7), subthreshold insomnia (8–14), moderate insomnia (15–21), and severe insomnia (22–28).

Depressive symptoms were screened using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), a 6-item tool specifically developed for PwE [31,32]. Each item is scored on a 4-point scale, with total scores ranging from 6 to 24. A score of 13.2 or above suggests the possibility of major depressive disorder and warrants further clinical evaluation [33].

Finally, health-related quality of life was assessed using the Quality of Life in Epilepsy Inventory (QoLIE-31) [34,35]. This 31-item questionnaire evaluates seven domains: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. Domain scores are transformed to a 0–100 scale, where higher scores represent better quality of life.

2.3. Statistical analysis

Sample size estimation was performed using G*Power 3.1.2. Based on a medium effect size (Cohen's $d = 0.50$), a significance level of $\alpha = 0.05$, and a statistical power of 0.95, the required minimum sample size

was calculated to be 45 participants.

Statistical analyses were conducted using SPSS Statistics (version 25; [36]). Parametric methods were applied, given that variables were normally distributed as confirmed by the Kolmogorov-Smirnov test. Repeated-measures analysis of covariance (ANCOVA) were used to assess changes between baseline and follow-up, adjusting for age, sex and seizure frequency at baseline. Correlation analyses were conducted using Pearson's correlation coefficient. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Participants enrolled and clinic-epileptological outcomes

A total of 74 participants (44.6 % male, mean age 42.41 ± 18.06 years) were enrolled in the study and completed the baseline visit. PER was added to a single ASM in 75.7 % of cases ($n = 56$) and to two or more concomitant ASMs in 24.3 % of cases ($n = 18$). At the follow-up visit at six months of treatment, 20.3 % of PwE ($n = 15$) discontinued PER, as they withdrew their consent to continue the study. No adverse events responsible for discontinuation were reported. In the 59 PwE who completed the visit at the follow-up, the median PER daily dose was 4.0 mg.

At the six-month follow-up, 45.76 % of PwE ($n = 27$) were seizure free. A reduction in seizure frequency of more than 75 % was observed in 5.08 % ($n = 3$) of PwE, whereas 27.12 % ($n = 16$) experienced a reduction of 50 %, while 3.39 % ($n = 2$) had a reduction of less than 25 %. No change in seizure frequency was reported by 6.78 % ($n = 4$) of PwE, and 11.86 % ($n = 7$) experienced worsening of seizures. The mean frequency of epileptic seizures significantly decreased from baseline to the six-month follow-up in the whole group (10.09 ± 19.88 vs. 5.93 ± 16.77 , $t = 3.313$, $p = 0.002$), indicating improved seizure control over time. Table 1 shows the demographic and clinical characteristics obtained at baseline.

3.2. Sleep results

Regarding sleep and daytime sleepiness, the PSQI global score improved from baseline to the six-month follow-up, also after adjusting for sex, age, and seizure frequency at baseline ($p = 0.001$). Specifically, significant improvements from baseline to follow-up were observed in the PSQI components of sleep duration ($p = 0.001$) and sleep efficiency ($p = 0.002$), and in the use of sleep medications ($p = 0.029$). Conversely, the components related to sleep latency, subjective sleep quality, sleep disturbances, and daytime dysfunction did not show significant changes over time.

Considering the 59 PwE who completed both baseline and six-month follow-up assessments, changes in sleep quality between baseline and the six-month follow-up were analysed by dichotomizing PSQI global scores based on the established cutoff score (PSQI ≥ 5 indicating poor sleep quality). At baseline, 34 (57.6 %) of the 59 PwE had poor sleep quality (PSQI ≥ 5), and this number decreased to 17 (28.8 %) at follow-up, with a significant shift ($\chi^2 = 11.008$; $p = 0.001$) (Table 3). Moreover, at follow-up, 30.5 % ($n = 18$) of PwE showed significant PSQI improvement, transitioning from PSQI ≥ 5 to PSQI < 5 (Table 3), while 40.7 % ($n = 24$) remained stable within the non-clinical range at both assessments. In contrast, 28.8 % ($n = 17$) did not improve, continuing to present the PSQI global score ≥ 5 .

The ISI score also significantly decreased over time, suggesting an overall improvement in insomnia symptoms, independent of sex, age, or seizure frequency ($F(1,55) = 10.076$, $p = 0.002$; Table 2). Regarding the changes in insomnia symptoms between baseline and the six-month follow-up by dichotomizing continuous variables based on the established cutoff score for the presence of insomnia symptoms, 27 (45.8 %) participants exhibited clinically significant insomnia symptoms (ISI ≥ 8) at baseline, which reduced to 18 (30.5 %) at follow-up ($\chi^2 = 21.990$, p

Table 1

PwE Demographic and Clinical Characteristics obtained at Baseline.

	Whole Group (n = 74) Mean $\pm$ SD	PwE who completed FU (n = 59) Mean $\pm$ SD	PwE who discontinued PER (n = 15) Mean $\pm$ SD
Age in years	42.41 $\pm$ 18.06	39.69 $\pm$ 18.38	52.93 $\pm$ 12.30
Sex, n. (%)	33 (44.6 %)	30 (50.8 %)	3 (20.0 %)
Males	29 (49.2 %)	29 (49.2 %)	12 (80.0 %)
Females	41 (55.4 %)		
Age at Epilepsy Onset	27.08 $\pm$ 18.87	26.19 $\pm$ 18.26	30.86 $\pm$ 21.61
Epilepsy Type, n (%)	43 (58.1 %)	33 (55.9 %)	10 (66.7 %)
Focal	9 (15.3 %)	9 (15.3 %)	3 (20.0 %)
Generalized	13 (17.6 %)	14 (23.7 %)	2 (13.3 %)
Focal and Generalized	2 (3.4 %)	2 (3.4 %)	0 (0.0 %)
Unknown	16 (21.6 %)		
Aetiology of Epilepsy, n. (%)	19 (25.7 %)	16 (27.1 %)	3 (20.0 %)
Structural	14 (18.9 %)	10 (16.9 %)	4 (26.7 %)
Genetic	2 (2.7 %)	2 (3.4 %)	0 (0.0 %)
Infectious	3 (4.1 %)	3 (5.1 %)	0 (0.0 %)
Immune	36 (48.6 %)	28 (47.5 %)	8 (53.3 %)
Unknown			
N° of previous ASM treatment, n. (%)	48 (64.9 %)	39 (66.1 %)	9 (60.0 %)
0	13 (22.0 %)	13 (22.0 %)	3 (20.0 %)
1	16 (21.6 %)	5 (8.5 %)	0 (0.0 %)
2	5 (6.8 %)	0 (0.0 %)	1 (6.7 %)
3	1 (1.4 %)	1 (1.7 %)	2 (13.3 %)
4	3 (4.1 %)	1 (1.7 %)	0 (0.0 %)
5	1 (1.4 %)		
N° of concomitant ASMs at the time of PER prescription, n. (%)	56 (75.7 %)	48 (81.4 %)	8 (53.3 %)
1	9 (15.3 %)	9 (15.3 %)	6 (40.0 %)
2 or more concomitant ASM	15 (20.3 %)	2 (3.4 %)	1 (6.7 %)
1			
2	3 (4.1 %)		
3			
PER as add-on, n. (%)	56 (75.7 %)	48 (81.4 %)	8 (53.3 %)
1 concomitant ASM	11 (18.6 %)	11 (18.6 %)	7 (46.7 %)
2 or more concomitant ASM	18 (24.3 %)		
Mean number of seizures at baseline	10.90 $\pm$ 20.72	10.09 $\pm$ 19.88	14.54 $\pm$ 24.71

Abbreviations: PwE, people with epilepsy; ASM, anti-seizure medication; PER, Perampanel; NA, not-applied; SD, Standard Deviation

< 0.001) (Table 3). Regarding the analysis evaluating the persistence of insomnia symptoms between baseline and follow-up, 17.0 % participants ($n = 10$) reported the improvement of insomnia symptoms, transitioning from ISI ≥ 8 to ISI < 8 , whereas 52.5 % ($n = 31$) remained stable below the clinical threshold at both time points. Meanwhile, 30.5 % ($n = 18$) did not improve, continuing to meet the ISI ≥ 8 global score.

ESS scores did not significantly change from baseline to follow-up ($F(1,53) = 0.759$, $p = 0.388$; Table 2). However, the excessive daytime sleepiness (ESS ≥ 10) was present in 12 PwE (20.3 %) at baseline and significantly decrease to 7 (11.9 %) at follow-up ($\chi^2 = 16.623$, $p < 0.001$; Table 3).

No significant time effects were observed for MEQ scores, suggesting that PER did not have a substantial effect on circadian sleep-wake rhythm preference over the study period.

Table 2 summarizes the changes in seizure frequency, sleep parameters, mood, and quality of life from baseline to the six-month follow-up.

3.3. Depressive symptoms and quality of life

Depressive symptoms measured by the NDDI-E scores did not change

Table 2

Changes in Seizure Frequency, Sleep Parameters, Mood, and Quality of Life from Baseline to the Six-Month Follow-Up.

	Time	Mean	SD	ANCOVA	Cohen's d
Mean number of seizures	Baseline	10.09	19.88	$t = 3.313, p = 0.002$	0.43
	6-month	5.93	16.77		
	Follow-up				
Global PSQI	Baseline	7.18	4.27	$F(1,53) = 11.800, p = 0.001$	0.94
	6-month	4.63	3.09		
	Follow-up				
C1. Subjective Sleep Quality	Baseline	1.22	0.83	$F(1,53) = 2.171, p = 0.147$	0.40
	6-month	0.98	0.82		
	Follow-up				
C2. Sleep Latency	Baseline	1.24	1.07	$F(1,53) = 2.238, p = 0.141$	0.41
	6-month	1.08	0.88		
	Follow-up				
C3. Sleep Duration	Baseline	0.93	0.93	$F(1,53) = 11.922, p = 0.001$	0.95
	6-month	0.10	0.55		
	Follow-up				
C4. Sleep Efficiency	Baseline	1.07	1.08	$F(1,53) = 10.582, p = 0.002$	0.95
	6-month	0.10	0.55		
	Follow-up				
C5. Sleep Disturbances	Baseline	1.24	0.57	$F(1,53) = 1.658, p = 0.203$	0.35
	6-month	1.07	0.55		
	Follow-up				
C6. Sleeping Medication	Baseline	0.70	1.18	$F(1,53) = 5.068, p = 0.029$	0.62
	6-month	0.42	1.00		
	Follow-up				
C7. Daytime Dysfunction	Baseline	0.77	0.96	$F(1,53) = 0.778, p = 0.382$	0.24
	6-month	0.86	0.88		
	Follow-up				
ISI	Baseline	8.15	6.23	$F(1,55) = 10.076, p = 0.002$	0.86
	6-month	5.32	5.25		
	Follow-up				
ESS	Baseline	6.49	3.93	$F(1,53) = 0.759, p = 0.388$	0.24
	6-month	5.63	3.55		
	Follow-up				
MEQ	Baseline	54.66	9.90	$F(1,53) = 1.050, p = 0.310$	0.28
	6-month	56.24	8.79		
	Follow-up				
NDDI-E	Baseline	11.32	4.13	$F(1,53) = 1.169, p = 0.284$	0.30
	6-month	10.51	3.54		
	Follow-up				
Seizure worry (QoLIE-31)	Baseline	42.80	28.12	$F(1,50) = 1.068, p = 0.306$	0.29
	6-month	52.14	24.03		
	Follow-up				
Overall quality of life (QoLIE-31)	Baseline	61.75	17.36	$F(1,50) = 4.533, p = 0.038$	0.60
	6-month	69.24	19.59		
	Follow-up				
Emotional well-being (QoLIE-31)	Baseline	60.83	20.26	$F(1,50) = 1.753, p = 0.191$	0.36
	6-month	64.88	19.82		
	Follow-up				
Energy/Fatigue (QoLIE-31)	Baseline	51.36	23.93	$F(1,50) = 3.284, p = 0.076$	0.51
	6-month	58.21	18.18		
	Follow-up				
Cognitive Function (QoLIE-31)	Baseline	60.79	26.73	$F(1,50) = 2.391, p = 0.128$	0.44
	6-month	69.17	25.17		
	Follow-up				
Medication effects (QoLIE-31)	Baseline	66.42	23.38	$F(1,50) = 0.082, p = 0.776^*$	0.09
	6-month	63.39	21.31		
	Follow-up				
Social Function (QoLIE-31)	Baseline	60.50	21.20	$F(1,50) = 5.309, p = 0.025$	0.65
	6-month	71.02	21.13		
	Follow-up				
Overall score QoLIE-31	Baseline	58.32	16.57	$F(1,50) = 4.801, p = 0.033$	0.62
	6-month	65.81	16.31		
	Follow-up				

Abbreviations: PSQI – Pittsburgh Sleep Quality Index; C – PSQI Component; ISI – Insomnia Severity Index; ESS – Epworth Sleepiness Scale; MEQ – Morningness–Eveningness Questionnaire; NDDI-E – Neurological Disorders Depression Inventory for Epilepsy; QoLIE-31 – Quality of Life in Epilepsy Inventory; ANCOVA – Analysis of Covariance; SD – Standard Deviation.

* Time $\times$ Sex interaction was significant ($p = 0.034$) for Medication Effects (QoLIE-31), however, post hoc analyses did not reveal significant within-sex-group changes over time.

between baseline and follow-up ($F(1,53) = 1.169, p = 0.284$; Table 2). In particular, considering the cutoff of the scale, 16 PwE (27.1 %) presented significant clinical symptoms at baseline, and this number reduced to 11 PwE (18.6 %) at follow-up ($\chi^2 = 3.582, p = 0.058$; Table 3).

The overall QoLIE-31 score improved ($p = 0.033$; Table 2), with notable positive effects on social functioning ($p = 0.025$) and overall quality of life ($p = 0.038$). However, no significant changes were observed in the other QoLIE-31 domains, including epilepsy-related concerns, emotional well-being, fatigue/energy levels, cognitive functioning, or medication effects.

3.4. Correlation analysis

The correlation analysis examined whether improvements in sleep quality (PSQI) and insomnia severity (ISI) were associated with changes in quality of life (QoLIE-31), excessive daytime sleepiness (ESS), depression (NDDI-E), and seizure frequency.

For PSQI improvement, no significant correlations were observed with quality of life ($p = 0.762$), daytime sleepiness ($p = 0.495$), or seizure frequency ($p = 0.548$); notably, a significant reduction in depressive symptoms was found ($p = 0.031$). Regarding ISI improvement, no significant correlations were observed with quality of life ($p = 0.796$), daytime sleepiness ($p = 0.802$), depression ($p = 0.645$), or seizure frequency ($p = 0.653$).

4. Discussion

The results of this real-world observational prospective multicentre study confirmed the effectiveness of PER as an early add-on treatment, and at low doses, in adult PwE. The primary aim of the study was confirmatory of previous findings. This study documented a significant reduction in mean seizure frequency across the entire PwE population. Furthermore, it confirmed prior real-world evidence by showing that more than one third of the participants achieved seizure freedom at the 6-month follow-up, suggesting the clinical potential of using PER as an early add-on treatment for refractory focal and generalized seizures. Notably, the present study proved the clinical potential of using PER also for controlling the other patient reported outcome, such as sleep disturbances, depressive symptoms and patients' well-being. The whole-group analysis documented the significant reduction of the PSQI and ISI scores, reflecting the improvement of sleep efficiency and quality and the amelioration of sleep fragmentation and insomnia, which are frequently reported complaints of PwE. A further relevant finding from this study was the significant reduction in the use of sleeping medications during the treatment with PER. This suggests that PER may act on mechanisms at the basis of sleep impairment in PwE, improving sleep quality in such a way as to reduce the need for using hypnotic medications. As a further result of the present study, the significant correlation between the improvement of sleep disturbances and the improvement of depressive symptoms further highlights the importance of targeting sleep quality in PwE for achieving the well-being. Accordingly, the overall increase of quality of life – evaluated with the specific scale for PwE – closed the virtuous cycle linking seizure control, sleep improvement, depressive symptoms reduction and the increase in

Table 3

Cutoff based analysis of significant changes of sleep and mood-related measures between baseline and follow-up.

	Baseline	Follow-up	p-value
	n (%)	n (%)	
PSQI (≥ 5)	34 (57.6 %)	17 (28.8 %)	0.001
ISI (≥ 8)	32 (44.6 %)	18 (30.5 %)	<0.001
ESS (≥ 10)	12 (20.3 %)	7 (11.9 %)	<0.001
NDDI-E (>13)	16 (27.1 %)	11 (18.6 %)	0.058

quality of life – in particular in social functioning.

The other subjective questionnaires submitted to the participants of the study documented the lack of changes in daytime sleepiness, measured by the ESS, although there was a significant reduction of PwE complaining for excessive daytime sleepiness from baseline to follow-up. Finally, no significant differences in circadian sleep-wake rhythm preferences, as measured by the MEQ, emerged during the observational period following PER prescription. Previous studies reported a significant higher incidence of adverse events such as somnolence following PER administration, in particular owing to the higher doses of the drug [37]. In the meantime, the clinical experience of physicians in using PER proved the beneficial effect of the drug when early used at low doses, as here reported, which also permits the high rate of good tolerability [38].

The improvement in sleep quality and well-being, however, can also be attributable to the mechanism of action of PER, as an AMPA antagonist. Accordingly, the inhibition of PER-mediated glutamatergic neurotransmission through selective blockade of AMPA receptors could indirectly influence GABAergic activity during sleep, contributing to a rebalance between excitation and inhibition in the central nervous system. This balance is crucial for the regulation of the sleep-wake cycle and, in particular, for the promotion of deep sleep.

The study described here has several strengths related to its design. Firstly, it allowed the collection of patient-reported outcomes on sleep following PER prescription, when used as an early add-on treatment and at low doses. Secondly, the multicentre nature of the study enabled the assessment of sleep-related outcomes in PwE enrolled across different regions of Italy. Thirdly, the prospective, longitudinal design over a six-month period was advantageous, as it allowed the observation of changes in sleep quality, daytime sleepiness, and sleep-wake patterns over time while minimizing the risk of retrospective bias. Another methodologically relevant aspect was the use of standardized and validated questionnaires, which ensured the reliability of measurements of sleep and related patient reported outcomes.

Conversely, the limitations of the present study include the lack of a control group and the absence of objective sleep measures, such as actigraphy or polysomnography, which could have provided more precise assessments of sleep patterns.

In conclusion, the improvements of sleep problems, insomnia symptoms and overall quality of life in the group of PwE starting PER and here presented, seem to reflect a combination of clinical and subjective benefits, resulting primarily from the seizure control and the better sleep quality. More regular and less fragmented sleep may contribute, in turn, to a reduction in hyperarousability, often associated with insomnia, with positive effects on maintaining the functional well-being. At the same time, decreasing the frequency of seizures may increase patients' perception of control over their clinical condition, reducing concerns related to the possibility of seizures in public settings. This increased feeling of mastery may attenuate anticipatory anxiety and the consequent avoidance of social situations, favouring fuller participation in daily life. These effects may also favourably impact on depressive symptoms, suggesting a close interconnection between neuropsychological aspects, sleep quality and quality of life. However, it must be considered that these results may be influenced by the relatively short duration of follow-up, and that further longitudinal studies will be necessary to confirm the stability of these benefits in the long term.

Data availability

Data will be available upon reasonable request to the corresponding author.

CRediT authorship contribution statement

G. Bergamo: Writing – original draft, Project administration, Data curation. **M. Fernandes:** Visualization, Formal analysis, Data curation. **S. Maio:** Resources. **G. Pauletto:** Resources. **A. Nilo:** Resources. **D.**

Arnaldi: Resources. **M. Puligheddu:** Resources. **L. Urso:** Resources. **F. Barbato:** Resources. **A. Cervellino:** Resources. **R. Renna:** Resources. **G. Boero:** Resources. **Nicola Pilolli:** Resources. **A. Giordano:** Resources. **P. Penza:** Resources. **M. Lieto:** Resources. **M. Pezzella:** Resources. **L. Giuliano:** Resources. **M.P. Pasolini:** Resources. **M. Piccioli:** Resources. **I. Barbaro:** Resources. **L. Fernando:** Visualization, Formal analysis, Data curation, Resources. **N.B. Mercuri:** Resources. **C. Liguori:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Funding

The present study received a research grant support from EISAI Ita.

Declaration of competing interest

The 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.

Acknowledgments

Claudio Liguori has received an unrestricted grant from Eisai S.r.l. for the study reported herein. The other Authors do not report disclosures related to this work.

References

- [1] Grigg-Damberger M, Foldvary-Schaefer N. Bidirectional relationships of sleep and epilepsy in adults with epilepsy. *Epilepsy Behav* 2021;116:107735.
- [2] Macêdo PJOM, de Oliveira PS, Foldvary-Schaefer N, da Gomes M, M.. Insomnia in people with epilepsy: a review of insomnia prevalence, risk factors and associations with epilepsy-related factors. *Epilepsy Res* 2017;135:158–67.
- [3] Liguori C, Spanetta M, Fernandes M, Izzi F, Placidi F, Mercuri NB. More than sleep and wake disturbances: an actigraphic study showing the sleep-wake pattern dysregulation in epilepsy. *Seizure* 2022;94:95–9.
- [4] Stirling RE, Hidajat CM, Grayden DB, et al. Sleep and seizure risk in epilepsy: bed and wake times are more important than sleep duration. *Brain* 2023;146(7):2803–13.
- [5] Wen Q, Wang Q, Yang H. The association between epilepsy and sleep disturbance in US adults: the mediating effect of depression. *BMC Public Health* 2024;24(1).
- [6] Liguori C, Toledo M, Kothare S. Effects of anti-seizure medications on sleep architecture and daytime sleepiness in patients with epilepsy: a literature review. *Sleep Med Rev* 2021;60:101559.
- [7] Liguori C, Toledo M, Kothare S. Effects of anti-seizure medications on sleep architecture and daytime sleepiness in patients with epilepsy: a literature review. *Sleep Med Rev* Published online 2021. 101559.
- [8] Bazil CW. Effects of antiepileptic drugs on sleep structure: are all drugs equal? *CNS Drugs* 2003;17(10):719–28.
- [9] Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime sleepiness: an evidence-based review of objective sleep metrics. *Epilepsia* 2014;55(1):26–37.
- [10] Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. *Sleep Med* 2003;4(1):51–5.
- [11] Löscher W, Schmidt D. Epilepsy: perampanel - new promise for refractory epilepsy? *Nat Rev Neurol* 2012;8(12):661–2.
- [12] Villanueva V, Montoya J, Castillo A, et al. Perampanel in routine clinical use in idiopathic generalized epilepsy: the 12-month GENERAL study. *Epilepsia* 2018;59(9):1740–52.
- [13] Rohrer A, Kalss G, Leitinger M, et al. Two-year real-world experience with perampanel in patients with refractory focal epilepsy: Austrian data. *Ther Adv Neurol Disord* 2016;9(6):445–53.
- [14] Rohrer A, Zimmermann G, Villanueva V, et al. Perampanel in routine clinical use across Europe: Pooled, multicenter, observational data. *Epilepsia* 2018;59(9):1727–39.
- [15] Morano A, Fattouch J, Albini M, et al. Perampanel as adjunctive therapy in highly refractory epilepsies: real-world data from an Italian tertiary care epilepsy centre. *J Neurol Sci* 2018;390(April):67–74.
- [16] Liguori C, Izzi F, Manfredi N, et al. Efficacy and tolerability of perampanel and levetiracetam as first add-on therapy in patients with epilepsy: a retrospective single center study. *Epilepsy Behav* 2018;80:173–6.
- [17] Fernandes M, Dainese F, Operto F, et al. Perampanel effectiveness and tolerability in patients with epilepsy at long-term follow-up. *Epilepsy Behav* 2021;121:108069.
- [18] European Medicines Agency. Fycompa: Summary of Product Characteristics.
- [19] US Food and Drug Administration. FYCOMPA® (perampanel) prescribing information. 2022.

- [20] Rocamora R, Álvarez I, Chavarría B, Principe A. Perampanel effect on sleep architecture in patients with epilepsy. *Seizure* December 2019;2020(76):137–42.
- [21] Toledo M, Gonzalez-Cuevas M, Miró-Lladó J, et al. Sleep quality and daytime sleepiness in patients treated with adjunctive perampanel for focal seizures. *Epilepsy Behav* 2016;63:57–62.
- [22] Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;58(4):512–21.
- [23] Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Maria P. Validity of the italian version of the pittsburgh sleep quality index (PSQI). Published online 2013: 511–9.
- [24] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
- [25] Vignatelli L, Plazzi G, Barbato A, et al. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci* 2003;23(6):295–300.
- [26] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540–5.
- [27] Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4(2):97–110.
- [28] Natale V. Validazione di una scala ridotta di Mattutinità (rMEQ). *Giunti Organizzazioni Speciali*. Published online; 1999.
- [29] Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601–8.
- [30] Castronovo V, Galbiati A, Marelli S, et al. Validation study of the italian version of the insomnia severity index (ISI). *Neurol Sci* 2016;37(9):1517–24.
- [31] Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 2006; 5(5):399–405.
- [32] Mula M, Iudice A, La Neve A, et al. Validation of the italian version of the neurological disorders depression inventory for epilepsy (NDDI-E). *Epilepsy Behav* 2012;24(3):329–31.
- [33] Kim DH, Kim YS, Yang TW, Kwon OY. Optimal cutoff score of the neurological disorders depression inventory for epilepsy (NDDI-E) for detecting major depressive disorder: a meta-analysis. *Epilepsy Behav* 2019;92:61–70.
- [34] Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-Item quality of life in epilepsy inventory. *Epilepsia* 1998;39(1):81–8.
- [35] Beghi E, Niero M, Roncolato M. Validity and reliability of the italian version of the quality-of-life in epilepsy inventory (QOLIE-31). *Seizure* 2005;14(7):452–8.
- [36] Ibm. SPSS - statistical package for social sciences. Published online 2020.
- [37] Bresnahan R, Hill RA, Wang J. Perampanel add-on for drug-resistant focal epilepsy. *Cochrane Database Syst Rev* 2023;2023(4).
- [38] Liu P, Zhu Z, Wu H. The safety of perampanel in different disorders and doses: a meta-analysis. *Seizure* 2023;106:22–8.