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Perampanel effect on sleep architecture in patients with epilepsy

Rodrigo Rocamora[a,b,*], Ion Álvarez[a], Beatriz Chavarría[a], Alessandro Principe[a,b]

[a] Epilepsy Monitoring Unit, Department of Neurology, Hospital del Mar Medical Research Institute, Carrer Aiguader, 88, 08003, Barcelona, Spain
[b] Faculty of Health and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain

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ABSTRACT

Purpose: Among patients with epilepsy, sleep disturbances can worsen seizure control. This prospective open-label study determined the effect of the antiepileptic drug perampanel on sleep architecture in patients with refractory epilepsy.

Methods: Adult patients with refractory epilepsy received add-on perampanel, starting at 2 mg/day at bedtime, increased by 2 mg after 2 weeks and then monthly until the target dose of 4–8 mg/day was reached. The median dose of perampanel used was 6 mg (SD 1.2). Polysomnographic (PSG) recordings were scheduled 1 week before starting perampanel and the control PSG after 12 weeks under perampanel treatment and at least 4 weeks on stable perampanel dose; patients completed the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) questionnaires. The main endpoints were change from baseline in the ESS and PSQI scores, and PSG variables.

Results: Of 25 patients included (aged 18–65 years, 56 % female) only 17 completed the study. Perampanel caused a modest decrease from baseline in mean ESS score (n = 13 patients; p = 0.126) and PSQI score (n = 12 patients; p = 0.127). Treatment significantly improved sleep parameters (n = 17 patients) including total sleep time (p = 0.037), sleep latency (p = 0.022), sleep efficiency (p = 0.015), sleep maintenance index (p = 0.005), wake time after sleep onset (p = 0.015), and duration of N3 sleep stage (p = 0.026). Patients with altered sleep efficiency parameters at baseline showed a significant increase in sleep maintenance index (p = 0.015), and 77.8 % achieved sleep efficiency > 85 % (p = 0.016 vs baseline).

Conclusion: Perampanel improved sleep architecture in patients with focal refractory epilepsy without worsening daytime sleepiness.

1. Introduction

In the modern society, focused on performance and achievement, the importance of sleep for good health is frequently ignored. The association between lack of sleep and the manifestation of epilepsy is also neglected, and physicians treating patients with epilepsy often do not have time and the necessary context to evaluate specific sleep disorders and associated symptoms. However, the impact of sleep on epilepsy (and vice versa) is complex and multifaceted [1]. Poor sleep quality or duration can worsen seizure control; seizures and epilepsy may also worsen sleep quality, thus establishing a vicious cycle [2,3]. Patients with epilepsy are also twice as likely to develop sleep disorders such as obstructive sleep apnea (OSA) and restless legs syndrome (RLS) compared with healthy individuals, contributing to further impairment of their quality of life [4].

The impact of antiepileptic drugs (AEDs) on sleep varies depending on the type of epilepsy [1,5]. Therefore, understanding the effects of AEDs on sleep may contribute to optimizing the management of epilepsy and its associated sleep disorders. Perampanel is a selective and non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist. In Europe, perampanel is approved as adjunctive therapy of partial-onset seizures with or without secondary generalization in adult and adolescent patients from 12 years of age and of primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy in the same age group [6]. Additionally, in the USA, perampanel has been approved as monotherapy or adjunctive

Abbreviations: AEMPS, Spanish Agency of Medicines and Health Products; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; OSA, obstructive sleep apnea; PSG-EEG, polysomnography-electroencephalography; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; SM, sleep maintenance; TST, total sleep time; WASO, wake time after sleep onset

* Corresponding author at: Epilepsy Monitoring Unit, Hospital del Mar, Passeig Maritim 25-29, E-08003, Barcelona, Spain.
E-mail addresses: rocamora@parcdesalutmar.cat (R. Rocamora), ialvarez@parcdesalutmar.cat (I. Álvarez), bchavarria@centromedicodelfos.es (B. Chavarría), alessandro.principe@upf.edu (A. Principe).

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therapy in the treatment of partial-onset seizures, with or without secondarily generalized seizures, in young patients with epilepsy (≥4 years of age) [7,8]. The efficacy and safety of perampanel (4–12 mg once daily [q.d.]) in the management of epilepsy has been reported [9–13], with its most common adverse event (AE) being somnolence [8,14]. Somnolence with perampanel may be due to the fact that its inhibitory target, the AMPA receptor, has a potential role in sleep regulation. Moreover, this effect of perampanel may be clinically beneficial, owing to the high prevalence of sleep disorders in patients with epilepsy and the protective effect of sleep maintenance in seizure prevention [3].

Preliminary evidence suggests that adjunctive perampanel in patients with focal seizures does not worsen sleep quality or daytime sleepiness after 3 months of treatment, and in fact reduces daytime sleepiness after 6 months of continued treatment [15]. In addition, low-dose perampanel is also reported to be a potential drug candidate for the treatment of idiopathic RLS [16]. The aim of the present study was to further understand the effects of perampanel on sleep in patients with focal epilepsy by assessing patient-reported daytime sleepiness and sleep quality, and the polysomnography-electroencephalography (PSG-EEG) recordings of patients taken before and after 12 weeks of treatment with perampanel (4–8 mg q.d.) and at least after 4 weeks under stable dose of perampanel.

2. Methods

2.1. Study design and participants

This prospective, open-label pilot study was conducted at the Epilepsy Monitoring Unit of Hospital del Mar, Barcelona, Spain. Patients were eligible for the study if they met the clinical criteria for epilepsy according to the International League Against Epilepsy (ILAE) [17] and were prescribed perampanel as an add-on therapy to routine treatment due to the lack of seizure control. The main exclusion criteria were: prior or current history of abuse/dependence on any substance with abuse potential according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR™); current diagnosis or history of psychotic disorder as defined in DSM-IV-TR™; clinical criteria of OSA or RLS; body mass index (BMI) > 30 kg/m^2; severe/acute respiratory failure or compromised respiratory function, or myasthenia gravis; sleep-wake cycle with a daytime sleep period of > 1 h on > 2 days a week; use of psychoactive or hypnotic drugs (including herbal medicines), antihistamines, opiates and opiate derivatives, itraconazole or rifampicin < 1 week prior to screening visit; use of depot antipsychotics < 6 months prior to screening visit; use of an investigational drug < 1 month prior to screening visit; consumption of > 5 caffeine-containing beverages or the nicotine equivalent of > 15 cigarettes a day; and taking > 3 AEDs prior to adjunctive perampanel therapy.

Baseline characteristics of patients who met the inclusion criteria were noted at their first visit to the outpatient clinic, along with their classification of epilepsy, current drug therapy, treatment compliance, and daytime sleepiness and sleep quality, as reported by patients using the Epworth Sleepiness Scale (ESS) [18] and the Pittsburgh Sleep Quality Index (PSQI) [19], respectively. The ESS has a maximum score of 24, with scores > 12 indicating moderate to severe daytime sleepiness [20]. The maximum PSQI score is 21 and scores < 5 are indicative of normal sleep quality [19,21].

All patients included in the study had their first PSG-EEG scheduled 1 week before starting perampanel therapy. Patients received a starting dose of 2 mg perampanel q.d. at bedtime, which was increased by 2 mg after 2 weeks and then monthly until it reached the primary target dose of 4–8 mg/day, depending on seizure control and tolerability. Patients underwent a second PSG-EEG per protocol after 3 months under perampanel treatment and at least 4 weeks after the target dose of 4–8 mg q.d. was achieved, and were also requested to complete the ESS and PSQI questionnaires. Provided that the main sleep disturbances reported in epilepsy are quality and duration, we arbitrarily chose a pattern of PSG abnormalities as specifically relevant that corresponded to an increased latency or decreased efficiency. The presence of those altered sleep parameters in PSG at baseline was defined as sleep efficiency < 85 % and/or sleep latency of > 20 min according to normal sleep parameters [22].

All AEDs taken by the patients before the study were maintained unchanged during the study period. The dose and titration schedule for perampanel were designed on a case-by-case basis depending on clinical criteria, and perampanel was never used with the intention of improving or modifying sleep characteristics. All collected data were stored securely using a database designed ad hoc and accessible only to the investigators to meet the privacy requirements for clinical data established by the Spanish laws.

The study was approved by the Spanish Agency of Medicines and Health Products (AEMPS) with code RRO-PER 2015-01 and was conducted in accordance with the Declaration of Helsinki code of ethics as adopted by the 18th World Medical Assembly in 1964 and subsequent amendments, and in accordance with Good Clinical Practice (GCP) guidelines, January 1997. The project was evaluated and approved by the Clinical Research Ethics Committee (CEIC-Parc de Salut Mar). All patients included in the study provided written informed consent.

2.2. Study endpoints

Primary endpoints of the study were the change in i) daytime sleepiness, as measured by ESS, and ii) quality of sleep assessed using PSQI; these were compared from baseline to the time point after which the patient had received 4 weeks of perampanel treatment with a target dose of 4–8 mg q.d. and per protocol always after 12 weeks under treatment with perampanel and 4 weeks on stable perampanel treatment. Secondary endpoints included: change from baseline in PSG-EEG variables such as time spent lying in bed, total sleep time (TST), sleep latency, sleep efficiency (the ratio of time spent lying in bed to actual time spent asleep), sleep maintenance index (SM), wake time after sleep onset (WASO) and duration of sleep stages.

As part of the clinical evaluation of the patients, the efficacy of the clinical response was monitored and the patients were classified as responders (≥50 % of seizure frequency reduction), seizure-free and non-responders (worsening, no change or < 50 % seizure frequency change). Similarly, the tolerability of the drug was evaluated based on the type and form of the adverse effects, as well as causes of discontinuation.

2.3. Statistical analyses

Measures of central tendency (mean and median) and variability (range and standard deviation [SD]) were used to describe the structure of sleep parameters before and after treatment with perampanel. ESS and PSQI scores were described numerically by the absolute frequency before and after perampanel treatment. Sleep parameters and sleep scores were compared using the Wilcoxon signed rank test or McNemar's test with the threshold of significance of $p < 0.05$. All statistical analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

A total of 25 patients (aged 18–65 years; 56 % female) met the study inclusion criteria. Eight patients never initiated/discontinued perampanel treatment due to the following reasons (note one patient met two of the following criteria): diagnosis of severe OSA not detected by the questionnaires ($n = 1$); increase in seizure frequency with

Table 1
Baseline characteristics of patients included in the study (n = 17). Data from ESS and PSQI were available in 13 patients.

Patient characteristics	n (%)
Age, years	
Mean ± SD	36.5 ± 10.3
Female	9 (52.9)
Type of epilepsy	
Focal onset seizures	16 (94.1)
Temporal lobe epilepsy	7 (41.2)
Frontal lobe epilepsy	7 (41.2)
Multifocal epilepsy	1 (5.9)
Parietal lobe epilepsy	1 (5.9)
Generalized epilepsy	1 (5.9)
Daytime sleepiness (ESS)	4 (30.8)
Quality of sleep (PSQI)	6 (46.2)
Subjective quality	10 (76.9)
Sleep latency	9 (69.2)
Duration of sleep	7 (53.8)

ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation.

perampanel (n = 2); status epilepticus before perampanel initiation (n = 1); refused perampanel treatment due to spontaneous control of seizures (n = 1); adverse effects such as somnolence (n = 2) or not specified (n = 1); and refused to perform second PSG after perampanel initiation (n = 1). All patients had refractory epilepsy with uncontrolled seizures, and all but one had focal onset seizures (Table 1). Seven patients had a diagnosis of temporal lobe epilepsy, seven frontal, one parietal, one with multifocal and generalized epilepsy, respectively (n = 17). The mean age was 36.5 years (SD 10.3), 9 were female. Of the 17 patients, 12 (70.6 %) were responders, defined as patients with a reduction in the baseline seizure-frequency higher than 50 %, and three (17.6 %) became seizure-free at 3 months with a median perampanel dose of 6 mg/day (SD 1.2).

A total of 17 patients completed the second PSG-EEG, and ESS and PSQI scores before and after perampanel treatment were obtained from 13 and 12 patients, respectively. Five patients had missing or incomplete questionnaires after their first PSG-EEG. All but one of the patients who completed the study presented with focal onset refractory epilepsy.

3.2. Daytime sleepiness

Of the initial 25 patients included, two dropped out due to reported daytime somnolence. For the remaining 17 patients who completed the study, ESS data were available for 13 patients, five of which reported daytime somnolence before perampanel. At the second evaluation, five out of 14 patients reported somnolence but only one of them was of new development; three patients maintained altered ESS scores and symptoms normalized in two patients. The mean (± SD) baseline ESS score was 9.2 ± 4.1 (n = 13) and 30.8 % of patients (n = 4) had a baseline ESS score of > 12 (Fig. 1). Treatment with perampanel did not cause a significant change from baseline in the mean ESS score (7.9 ± 3.9; p = 0.126). Only 15.4 % of patients (n = 2) experienced moderate-to-severe daytime sleepiness (ESS > 12) with perampanel; this effect was not statistically significant (p = 0.5).

3.3. Quality of sleep

The mean (± SD) baseline total PSQI score was 8.6 ± 6.6 (n = 12), and 50 % of patients (n = 6) had scores > 5 indicating global sleep quality reduction. Treatment with perampanel did not cause a significant change from baseline in the mean PSQI score (7.0 ± 4.8; p = 0.127).

When the PSQI components were analyzed separately in patients with normal (< 5) and abnormal (> 5) scores before perampanel treatment, no significant differences were observed in subjective sleep quality (p = 0.129), sleep latency (p = 0.527), sleep duration (p = 0.408), sleep efficiency (p = 0.102), sleep disturbances (p = 0.564), use of hypnotics (p = 0.892) or daytime somnolence in either group (p = 0.589; Supplementary Fig. 1). Perampanel also did not cause a significant change from baseline in the number of patients with abnormal global sleep quality score (n = 6; p = 1.000).

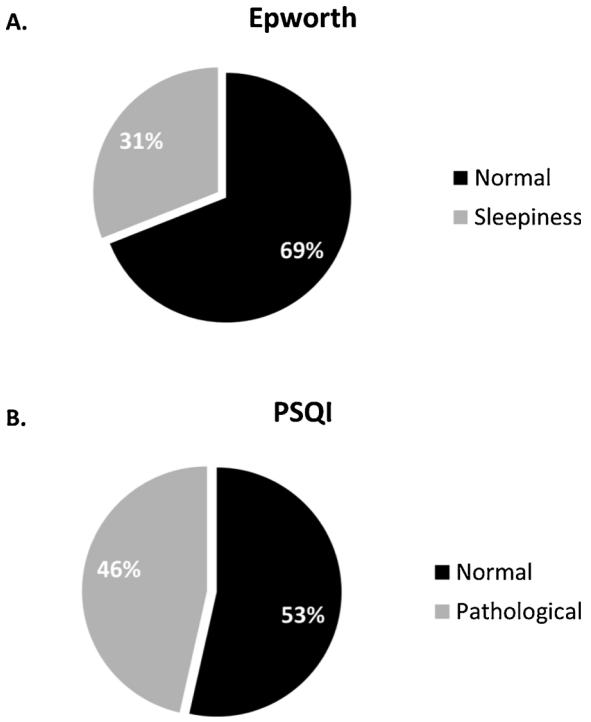

Fig. 1. Proportion of patients with daytime sleepiness. **A.** ESS score of > 12 and **B.** PSQI score ≥ 5 at baseline.

3.4. Polysomnographic recordings

Among the 17 patients whose PSG-EEG were available before and after perampanel treatment, 52.9 % patients (n = 9) presented with baseline pathological sleep parameters of sleep latency or sleep efficiency as previously defined before perampanel treatment.

Time spent lying in bed was similar at baseline and during perampanel treatment (mean duration before vs. after: 425.0 ± 38.9 min vs. 439.1 ± 39.4 min; p = 0.093). This duration was also similar after perampanel treatment among patients with pathological (428.6 ± 36.2 min vs. 440.4 ± 46.1 min; p = 0.314) or normal (422.1 ± 44 min vs. 437.7 ± 33.5 min; p = 0.208) sleep parameters at baseline.

Total sleep time increased significantly with perampanel treatment (mean duration before vs. after: 362.8 ± 47.1 min vs. 399.8 ± 52.2 min; p = 0.037). A similar trend was seen in the subgroups of patients with versus without pathological sleep, but the change from baseline in these subgroups did not reach statistical significance: total sleep time among patients with pathological sleep (341.2 ± 40.2 min vs. 387.4 ± 52.2 min; p = 0.110) or normal (387 ± 44.3 min vs. 413.8 ± 39.2 min; p = 0.208) sleep at baseline.

Sleep latency was also significantly reduced with perampanel treatment (mean duration before vs. after: 15 ± 6.9 min vs. 6.2 ± 5.7 min; p = 0.022). Of the 17 patients, four (23.5 %) took ≥ 20 min to fall asleep at baseline versus one (5.9 %) after perampanel treatment. Perampanel treatment did not cause significant differences in sleep latency among patients with pathological sleep parameters at baseline (19.2 ± 22.5 min vs 7.8 ± 6.3 min; p = 0.314). Among

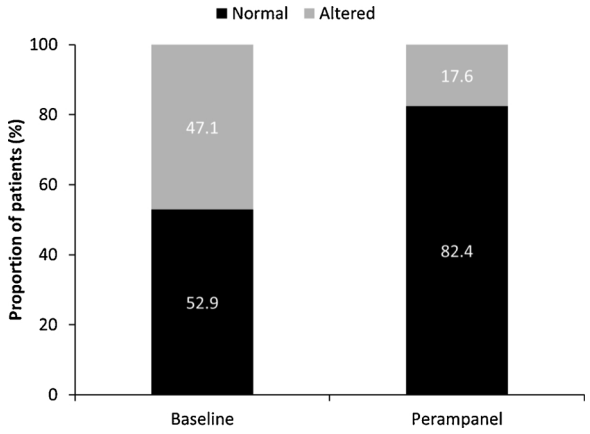

Fig. 2. Proportion of patients with normal and reduced sleep efficiency (< 85 %) before and after 12 weeks of perampanel treatment and 4 weeks under stable treatment (target dose 4–8 mg q.d.).

patients with normal sleep at baseline, treatment with perampanel led to a significant reduction in sleep latency (10.2 ± 4.5 min vs. 4.5 ± 4.6 min; $p = 0.012$).

Sleep efficiency increased significantly with perampanel treatment (before vs. after: 85.3 ± 7.7 % vs. 91.9 ± 7.8 %; $p = 0.015$). The proportion of patients with normal and reduced sleep efficiency (defined as < 85 %) in the two conditions is shown in Fig. 2. Patients with pathological or normal sleep parameters at baseline did not show significant differences in the mean sleep efficiency after perampanel treatment. Among patients with altered parameters at baseline ($n = 9$), 77.8 % achieved sleep efficiency > 85 % after perampanel treatment ($p = 0.016$ vs baseline).

Perampanel also caused a significant increase in the sleep maintenance index, defined as the total time asleep as a proportion of total time in bed after sleep onset (mean before vs. after: 88.7 ± 7.4 % vs. 94 ± 4.9 %; $p = 0.005$). A significant increase in the sleep maintenance index was also observed among patients with abnormal parameters at baseline (84.4 ± 7.5 % vs. 92.6 ± 4.7 %; $p = 0.015$) but not among patients with normal sleep at baseline (93.6 ± 3 % vs. 95.4 ± 5 %; $p = 0.161$).

The duration of WASO (not including sleep latency) also decreased significantly with perampanel treatment (mean duration before vs. after: 63.2 ± 34.1 min vs. 39.7 ± 36.3 min; $p = 0.015$). The decrease in WASO among patients with abnormal sleep parameters (mean duration before vs. after: 87.8 ± 28.1 min vs. 53.3 ± 42.7 min; $p = 0.110$) and normal sleep at baseline (35.4 ± 10.1 min vs. 24.4 ± 20.5 min; $p = 0.123$) was not statistically significant.

There were no significant differences in the number of awakenings (transitions from sleep to awakening) or micro-awakenings (short duration awakenings lasting a fraction or few seconds which did not lead to a full awakening) among patients treated with perampanel, irrespective of their pathological or normal sleep status at baseline (Supplementary Fig. 2).

3.5. Analysis of sleep phases

Perampanel significantly increased the duration of the N3 sleep stage ($n = 17$; $p = 0.026$); (Fig. 3). This increase in the duration of deep sleep (N3) was achieved concomitantly with a significant reduction in awake time ($n = 17$; $p = 0.015$). The duration of N1, N2 or rapid eye movement (REM) stages of sleep showed no significant changes from baseline with perampanel (Fig. 3). No significant difference was observed in REM sleep latency among the total study population, and among patients with normal or pathological sleep at baseline (data not shown).

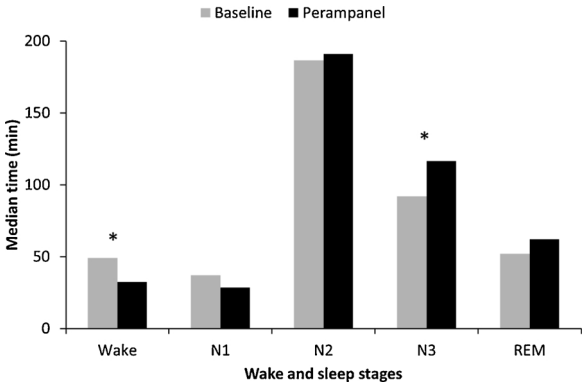

Fig. 3. Median duration of wake and sleep stages (N1, N2, N3 and REM) before and after 12 weeks of perampanel treatment and 4 weeks with a stable dose (4–8 mg q.d.). *$p < 0.05$.

4. Discussion

This prospective pilot study determined the effect of perampanel treatment on sleep architecture in 17 patients with refractory epilepsy. After being titrated to 4 weeks of treatment with perampanel 4–8 mg q.d. and per protocol after 12 weeks under treatment with perampanel (and 4 weeks with stable perampanel treatment), total sleep time, sleep efficiency, sleep maintenance index, and duration of the N3 sleep stage significantly increased, while wake time, sleep latency and WASO significantly decreased. Modest and non-significant changes from baseline were observed in daytime somnolence and sleep quality among the treated patients, although the study was not primarily designed to evaluate those parameters.

Lack of sleep has deleterious effects on daily cognitive function. One potential mechanism that may be altered by sleep deprivation is the function of glutamatergic AMPA receptors, the receptors that mediate the majority of fast excitatory transmission in the central nervous system and are closely involved in mnemonic processes and hippocampal synaptic plasticity [23]. Sustained increases in extracellular glutamate concentrations have been reported in patients with epilepsy, measured prior to and during seizure activity [24]. Monti and colleagues reported increased slow wave sleep and prevention of the REM suppression using NMDA and AMPA/kainate receptor antagonists in rat models [25]. However, scarce data are currently available regarding the effect of glutamate antagonism on sleep physiology in humans. The results of the present study show that 12-week treatment with perampanel (4–8 mg q.d.), an AMPA antagonist, increased total sleep time and reduced sleep latency in these patients, as seen in their PSG recordings. Perampanel also significantly increased the duration of deep sleep (N3 phase) coupled with a significant reduction of wake time during the night, and improved sleep efficiency and the sleep maintenance index, particularly among patients with low sleep efficiency, and reduced WASO, but did not affect the number of awakenings or micro-awakenings. However, classic PSG analysis as performed in our work, is not the most appropriate for assessing the stability of sleep, so we prefer not to draw conclusions in this regard. To further understand this a study could be performed to analyze cyclic alternating patterns (CAP) that reflects specifically the stability of the physiological regulation of the sleep structure; but it was outside the scope of our initial evaluation.

These results suggest that perampanel may have a positive profile in the modulation of sleep patterns in this patient population, although further studies in larger patient populations are required to confirm this effect.

The efficacy and tolerability of perampanel in patients with refractory partial-onset seizures has been reported in randomized dose-escalation studies [24]. Despite somnolence being one of the most

common side effects reported with perampanel [8,14], the EES and PSQI scores obtained during the present study indicate that perampanel did not increase daytime sleepiness or reduce the quality of sleep in patients with refractory epilepsy with focal-onset seizures. Indeed, measures of daytime somnolence were relatively stable throughout the study: prior to perampanel treatment five patients reported daytime somnolence; at the second evaluation, five patients also reported daytime somnolence, though somnolence presented for the first time/was a new development during perampanel treatment in one of these patients. This incongruence in the prevalence of daytime sleepiness between our study and previous reports is probably related to use of specific sleep questionnaires in which patients can discriminate symptoms like dizziness or fatigue from somnolence itself. However, it should also be noted that our study was not designed to evaluate change in ESS.

Results of the present study were based on outcomes after patients with focal epilepsy had received 12 weeks of perampanel treatment with target dose of 4–8 mg q.d.; however, the onset of these effects was not studied. In a similar study, de Hass and colleagues compared the effect of 300 mg/day of pregabalin on sleep in patients with epilepsy [26]. In this randomized case-control study, the authors found after a 4-week treatment that WASO tended to improve in the pregabalin group compared with placebo. However, no change in self-reported seizures was found.

Therefore, further studies are needed to determine the onset of the effect of perampanel on sleep architecture, and whether the AEs of perampanel decrease with prolonged treatment. Also, the duration of this effect of perampanel needs to be determined, along with understanding whether these effects are likely to wear off with long-term perampanel treatment.

Due to the study design with only 17 cases evaluated, our analysis did not allow establishing a clear relationship between responders (reduction in self-reported seizure frequency $\geq$50 %) and sleep modulation. In the whole group, 12 patients were considered responders and 3 were seizure-free, and due to the small number of patients in each group we did not perform any statistical analysis. However, the global clinical impression was that the effect of perampanel was similar in both groups.

Therefore, it is possible that the mechanism of the effect of perampanel on sleep may be independent of its antiepileptic effect, similar to the study by García-Borreguero and colleagues, which suggested that the efficacy of perampanel in idiopathic RLS may be due to its glutamatergic mechanism of action [16]. Once the effects of perampanel on sleep architecture are confirmed, perampanel could be a suitable candidate for the management of patients with focal epilepsy who have sleep complaints, specifically those related to poor sleep quality or insomnia.

This is the first study to examine PSG recordings of patients before and after perampanel treatment in patients with focal epilepsy who had normal and pathological sleep at baseline. However, the study has several limitations. Firstly, the study included a small sample size, uncontrolled study design and allowed the use of concomitant AEDs that may have caused specific sleep modifications. Moreover, the lack of prolonged recordings through video-EEG and the reduced sample did not allow us to improve neurophysiological effects on seizure control. However, such a design would have made the study difficult to perform because it was specifically focused on the physiology of sleep. On the other hand, although epileptic seizures were specifically ruled out during the PSG evaluation, due to the montage of a sleep study we cannot completely rule out the presence of epileptic arousals. To rule out this aspect, the use of a 10–20 assembly such as the classic video-EEG would have been necessary. Secondly, limb activity was not monitored during the study to determine the effect of perampanel on periodic leg movements. Finally, the study used a single PSG at each assessment (before and after 12 weeks of perampanel) which may have introduced bias of first-night effect.

5. Conclusion

Perampanel (4–8 mg q.d.) significantly decreased sleep latency and WASO, and increased sleep efficiency and deep sleep, but did not affect subjective parameters of sleep quality or daytime sleepiness. These data suggest that perampanel may be an AED with sleep-promoting effects, which are especially important considering the prevalence of sleep disorders in patients with epilepsy, and the potential protective effect of sleep maintenance on seizure prevention. Further studies with a larger patient population are warranted.

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Author contributions

Rodrigo Rocamora was responsible for the design and conceptualization of the study. Mónica Hoyos was involved in the preparation and editing of the manuscript. All authors were involved in the data acquisition, analysis and interpretation, and reviewing the manuscript before submission.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.01.021.

References

[1] Bazil CW. Sleep and epilepsy. Semin Neurol 2017;37(4):407–12. https://doi.org/10.1055/s-0037-1604352.
[2] Mendez M, Radtke RA. Interactions between sleep and epilepsy. J Clin Neurophysiol 2001;18(2):106–27.
[3] Rocamora R, Andrzejak RG, Jimenez-Conde J, Elger CE. Sleep modulation of epileptic activity in mesial and neocortical temporal lobe epilepsy: a study with depth and subdural electrodes. Epilepsy Behav 2013;28(2):185–90. https://doi.org/10.1016/j.yebeh.2013.04.010.
[4] Ismayilova V, Demir AU, Tezer FI. Subjective sleep disturbance in epilepsy patients at an outpatient clinic: a questionnaire-based study on prevalence. Epilepsy Res 2015;115:119–25. https://doi.org/10.1016/j.eplepsyres.2015.06.009.
[5] 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. https://doi.org/10.1111/epi.12478.
[6] European Medicines Agency. FYCOMPA® (perampanel) authorisation details. 2012https://www.ema.europa.eu/en/medicines/human/EPAR/fycompa#authorisation-details-section.
[7] Eisai. FYCOMPA® newly approved by USFDA as treatment for partial-onset seizures in pediatric patients with epilepsy. 2018 Accessed 21 May 2019 https://www.eisai.com/news/2018/news201879.html.
[8] US Food and Drug Administration. FYCOMPA® (perampanel) prescribing information. 2018https://www.fycompa.com/-/media/Files/Fycompa/Fycompa_Prescribing_Information.pdf.
[9] Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al.

Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78(18):1408–15. https://doi.org/10.1212/WNL.0b013e318254473a.
[10] Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Clement JF, et al. Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307. Epilepsia 2014;55(7):1058–68. https://doi.org/10.1111/epi.12643.
[11] French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012;79(6):589–96. https://doi.org/10.1212/WNL.0b013e3182635735.
[12] French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia 2013;54(1):117–25. https://doi.org/10.1111/j.1528-1167.2012.03638.x.
[13] Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia 2013;54(8):1481–9. https://doi.org/10.1111/epi.12212.
[14] European Medicines Agency. FYCOMPA® Summary of product characteristics. 2017https://www.ema.europa.eu/en/documents/product-information/fycompa-epar-product-information_en.pdf.
[15] Toledo M, Gonzalez-Cuevas M, Miro-Llado J, Molins-Albanell A, Falip M, Martinez AB, et al. Sleep quality and daytime sleepiness in patients treated with adjunctive perampanel for focal seizures. Epilepsy Behav 2016;63:57–62. https://doi.org/10.1016/j.yebeh.2016.08.004.
[16] Garcia-Borreguero D, Cano I, Granizo JJ. Treatment of restless legs syndrome with the selective AMPA receptor antagonist perampanel. Sleep Med 2017;34:105–8. https://doi.org/10.1016/j.sleep.2017.03.012.
[17] Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58(4):531–42. https://doi.org/10.1111/epi.13671.
[18] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5. https://doi.org/10.1093/sleep/14.6.540.
[19] Buysse DJ, Reynolds 3rd 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.
[20] Sharafkhaneh A, Hirshkowitz M. Contextual factors and perceived self-reported sleepiness: a preliminary report. Sleep Med 2003;4(4):327–31.
[21] Rico AR, Fernández JM. Propiedades clinimétricas de la versión castellana del cuestionario de Pittsburg. Vigilia-Sueño 1997;9(2):81–94.
[22] Merica H, Gaillard JM. Statistical Description and evaluation of the interrelationships of standard sleep variables for normal subjects. Sleep 1985;8(3):261–73.
[23] Dubiela FP, Queiroz CM, Moreira KD, Nobrega JN, Sita LV, Tufik S, et al. AMPA receptors mediate passive avoidance deficits induced by sleep deprivation. Behav Brain Res 2013;257:189–96. https://doi.org/10.1016/j.bbr.2013.09.037.
[24] Krauss GL, Bar M, Biton V, Klapper JA, Rektor I, Vaiciene-Magistris N, et al. Tolerability and safety of perampanel: two randomized dose-escalation studies. Acta Neurol Scand 2012;125(1):8–15. https://doi.org/10.1111/j.1600-0404.2011.01588.x.
[25] Monti JM, Jantos H, Catenaccio V, Xavier S. Blockade of the NMDA and AMPA/kainate receptors in the dorsal raphe nucleus prevents the 5-HT(3) receptor agonist m-chlorophenylbiguanide-induced suppression of REM sleep in the rat. Prog Neuropsychopharmacol Biol Psychiatry 2011;35(5):1341–8. https://doi.org/10.1016/j.pnpbp.2011.04.001.
[26] de Haas S, Otte A, de Weerd A, van Erp G, Cohen A, van Gerven J. Exploratory polysomnographic evaluation of pregabalin on sleep disturbance in patients with epilepsy. J Clin Sleep Med 2007;3(5):473–8.