



## Case Report

## Effect of adjunctive perampanel on the quality of sleep and daytime somnolence in patients with epilepsy



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## ABSTRACT

This prospective uncontrolled study evaluated the effect of low-dose adjunctive perampanel therapy (4 mg/day for 3 months) on the sleep-wake cycle and daytime somnolence in adult patients (n = 10) with focal seizures. A >50% reduction in the number of seizures was reported in 80% of the study patients; treatment had no significant effect on any sleep parameters as evident by the Maintenance of Wakefulness Test, Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale scores. Two patients reported dizziness with treatment. In conclusion, low-dose perampanel may improve seizure control without affecting the sleep characteristics or daytime somnolence in patients with epilepsy.

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## 1. Introduction

Perampanel is a non-competitive antagonist of the AMPA receptor approved for the adjunctive treatment of epilepsy [1]. Data from pivotal clinical trials and real-life studies show that perampanel causes effective reduction in the number of seizures [2,3]. However, one of the main concerns with the use of perampanel is the treatment-associated somnolence which is the main reason for the drug being recommended at bedtime [1].

Sleep architecture and daytime somnolence can be assessed using different methods. The use of subjective assessments has been reported in studies with large number of patients; however, objective methods have shown better reliability [4,5]. Home actigraphy for 1–2 weeks in combination with the maintenance of wakefulness test (MWT) are the most commonly used objective methods that are reported to be useful in determining the effects of a treatment on sleep and daytime

sleepiness [6]. These tests serve as low-cost, non-invasive, longitudinal methods for the diagnostic and post-treatment evaluation of sleep in ambulatory settings [6]. Polysomnography can also be used to determine the impact of a treatment on sleep architecture; however the complexity and cost of this assessment limit its use [7].

All anti-seizure drugs (ASDs) have a potential impact on sleep architecture and daytime somnolence. Studies have suggested that newer ASDs may have favorable effects on the sleep-wake cycle than the older ones [8,9]. However, no objective studies have explored the effect of perampanel on sleep. The present study assessed the impact of adjunctive perampanel therapy on the quality of sleep and daytime somnolence in patients with epilepsy and evaluated the treatment-associated AEs.

## 2. Material and methods

This prospective non-interventional study included patients aged > 16 years who had epilepsy with focal seizures, were on stable treatment with ≥ 1ASD for at least 3 months for which a clinical decision for initiating perampanel therapy was taken. Patients with progressive diseases, major psychiatric disorders, history of non-epileptic seizures, intake of drugs interfering with the CNS other than ASDs and evidence of sleep disorders were excluded.

A full anamnesis including the seizure type and frequencies in the past 3 months was performed at the baseline visit. Further, a pre-treatment sleep assessment was performed in all patients before

*Abbreviations:* ASDs, anti-seizure drugs; AEs, adverse events; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS, central nervous system; ESS, Epworth sleepiness scale; MWT, maintenance wakefulness test; PSQI, Pittsburgh sleep quality index; REM, rapid eye movement.

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initiating the perampanel therapy using the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and 1 week of domiciliary actigraphy followed by the MWT. Perampanel was added to baseline ASDs and given once daily at bedtime with a starting dose of 2 mg increasing to 4 mg after the first 2 weeks. At the end of 3-month treatment period, all patients on stable-dose perampanel and unchanged baseline ASD scheme underwent a follow-up which included the same sleep assessments as at baseline. Any dose adjustment during follow-up was based on the seizure control and tolerability of perampanel.

The ESS and the PSQI scores were considered normal for values below 10 and 5, respectively. Actigraphy was performed using a continuous wristwatch like actigraph (Actiwatch MiniMitter) that measured the 3D movements in the non-dominant limb; data were processed using the Actiware sleep software version 5.3 (MiniMitter Company) to determine the sleep latency (first 10-min period with <2 epochs of activity), sleep time (sum of time of epochs not exceeding the sensitivity threshold), sleep efficiency (sleep time divided by the time in bed multiplied by 100), wake after sleep onset (total time awake after the first sleep onset period) and the movement and fragmentation index (number of 1-min periods of immobility relative to the total number of immobility phases).

The MWT was performed on the day the patients returned the actigraph in order to objectively test daytime somnolence and consisted of four trials performed at 2-h intervals, with the first trial beginning about 1.5 h after the patient's usual wake-up time. The MWT recordings included electroencephalogram derivations (C3-A2, C4-A1, O1-A2 and O2-A1), electrooculograms, chin electromyogram and electrocardiogram. Patients were asked to sit still and remain awake for as long as possible. Sleep onset was defined as the first epoch of > 15 s of cumulative sleep in a 30-s epoch. Trials ended after 40 min if no sleep occurred or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep. The mean sleep latency from all sessions and the number of sleep-onset rapid eye movement (REM) periods during the MWT were calculated for each patient.

The study was approved by the Local Ethics Committee (mat-lev-2014-01) and all patients included in the study provided a written informed consent.

### 2.1. Statistical methods

Descriptive and frequency statistical analysis were performed and comparisons were made using the SPSS Statistics software Version 17.0. Wilcoxon signed ranks test was used to assess changes in the actigraphy values and the PSQI and ESS scores. A p-value of <0.05 was considered as statistically significant.

## 3. Results

Of the 13 patients enrolled in the study, three were excluded due to discontinuation of perampanel treatment: reasons included insufficient response in one patient and dizziness in two patients. Baseline demographics and the clinical data of the patients included in the study are shown in Table 1.

Perampanel was administered at a dose of 4 mg/day in all patients. The concomitant ASDs used were oxcarbazepine (n = 3); levetiracetam, lacosamide, eslicarbazepine and carbamazepine (n = 2 each); and phenytoin, lamotrigine, phenobarbital and zonisamide (n = 1 each). At the end of 3-month treatment, eight patients (80%) showed a seizure reduction of >50%, of which three were seizure-free and two reported persistent mild dizziness related to perampanel treatment. No other AEs were reported.

The baseline assessments of nocturnal sleep, actigraphy, PSQI scores and MWT and ESS scores were within normal limits. Following 3 months of perampanel treatment, no significant changes in sleep assessments were observed (Table 2). MWT was performed at a median time of 8.5 h (range 8–9.5 h) after the last dose of perampanel during

**Table 1**  
Patients demographics and baseline clinical characteristics.

Characteristics	N = 10 (%)
Age, years (mean ± SD)	40.10 ± 14.6
Male, n (%)	5 (50)
Seizure frequency/month, median (IQR)	2 (1–16)
Number of concomitant ASDs	
1	4 (40)
2	3 (30)
3	3 (30)
Seizure etiology, n (%)	
Unknown	4 (40)
Mesial temporal sclerosis	2 (20)
Trauma	2 (20)
Malformation of cortical development	1 (10)
Meningitis	1 (10)
Seizure type, n (%)	
Simple partial	4 (40)
Complex partial	7 (70)
Secondary generalized	2 (20)
Seizure origin, n (%)	
Frontal	4 (40)
Temporal	6 (60)

ASD, anti-seizure drug; IQR: interquartile range; SD, standard deviation.

the follow-up assessment in all patients. A reduction in each component of the PSQI scores was observed with treatment; these differences were not statistically significant (Table 2). No sleep-onset REM periods were observed before or after treatment.

## 4. Discussion

The present exploratory study determined the effect of low-dose adjunctive perampanel therapy on somnolence and sleep in patients with epilepsy. Perampanel was well tolerated; no sleep disturbances were observed nor were there any changes in sleep parameters.

Several studies have explored the effect of ASDs on sleep characteristics [8,9]. However, data from these studies is not robust due to the uncontrolled nature of these trials. This study was based on an exploratory approach focused to understand the impact of perampanel on the quality of sleep and daytime somnolence in patients with epilepsy. Treatment reduced the number of seizures with no significant modifications in the objective and subjective assessments of the quality of sleep and somnolence.

Perampanel is recommended at bedtime due to a potential risk of somnolence [1,10,11]. Additional risk factors associated with increased daytime somnolence in patients with epilepsy are ASD polytherapy

**Table 2**  
Nocturnal and daytime sleep assessments at baseline and after 3 months of treatment with perampanel 4 mg/day (N = 10).

Sleep assessments	Baseline (mean ± SD)	Perampanel treatment (mean ± SD)	p-Value
Actigraphy sleep values			
TST (min)	430.10 ± 63.08	438.70 ± 55.96	0.441
Sleep latency (min)	10.87 ± 8.25	16.03 ± 12.67	0.241
Sleep efficiency (%)	91.36 ± 3.60	89.27 ± 4.91	0.093
PSQI score			
Global score	4.10 ± 3.72	3.60 ± 3.89	0.357
Subjective sleep quality	0.80 ± 0.92	0.60 ± 0.70	0.317
Sleep latency	0.90 ± 0.88	0.80 ± 1.23	0.739
Sleep duration	0.70 ± 1.06	0.60 ± 0.84	0.564
Sleep efficiency	0.50 ± 0.97	0.70 ± 1.25	0.317
Sleep disturbances	0.70 ± 0.48	0.50 ± 0.53	0.157
Sleeping medication	0.00 ± 0.00	0.10 ± 0.32	0.317
Daytime dysfunction	0.50 ± 0.70	0.30 ± 0.67	0.157
ESS score	4.70 ± 3.65	3.80 ± 4.21	0.323
MWT (minutes)	24.10 ± 10.72	24.10 ± 11.97	0.799

ESS, Epworth sleepiness scale; MWT, maintenance wakeful test; PSQI, Pittsburgh sleep quality index; SD, standard deviation; TST, total sleep time.

and the presence of uncontrolled seizures [12]. Somnolence is a dose-dependent AE reported in 12–18% of patients taking perampanel [3, 13]. Also, daytime somnolence is reported in 11–28% of patients with focal epilepsy [12]. The results of this study did not show any effect of perampanel on the sleep latency; this may be due to the fact that the study included patients with healthy sleep characteristics with no significant somnolence at baseline and used lower doses of perampanel than reported in pivotal studies [2] along with a high rate of seizure responders observed in the study, which may have introduced bias in the results.

The prospective data evaluation during this exploratory study and the use of combined objective and subjective tests carried at a single center are the major strengths of the study. Conversely, the open-label, uncontrolled study design and the small sample size are the main limitations. Also, the MWT was performed long after perampanel intake; it would be interesting to perform the test immediately after perampanel intake to confirm the peak-of-dose somnolence effect of the drug. The use of polysomnography could also have provided information on the impact of perampanel treatment on sleep architecture.

The present study was based on the hypothesis that low-dose perampanel may have a beneficial effect on the sleep patterns of patients with epilepsy. However, due to the relatively short duration of the study and healthy sleep profile of the study population, the results do not support the initial hypothesis.

## 5. Conclusion

The present study suggests that low-dose adjunctive perampanel therapy in patients with epilepsy may improve the control of seizures without affecting their sleep characteristics or causing daytime sleepiness. Further randomized, placebo-controlled studies with multiple treatment groups to study the collateral effects of ASDs are warranted.

## Conflicts of interest

MGC, MT, ES and XS have received funding and honoraria from Eisai Pharmaceuticals, UCB Pharma, BIAL, GSK and Esteve.

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