Pharmacological differences of GABAergic compounds: a pharmacodynamic characterization

Haas, S.L. de

CHAPTER 10

Exploratory Polysomnographic Evaluation of Pregabalin on Sleep Disturbance in Patients with Epilepsy

Journal of Clinical Sleep Medicine 2007 3(5): 473-478

Sanne de Haas[1], Andreas Otte[2], Al de Weerd[3], Gerard van Erp [4], Adam Cohen[1], Joop van Gerven[1]

1 Centre for Human Drug Research (CHDR), Leiden, The Netherlands
2 International Medical Research, Pfizer Group Pharmaceuticals, Freiburg, Germany
3 Centre for Sleep & Wake Disorders, Medical Centre Haaglanden, Westeinde Hospital, The Hague, The Netherlands
4 Epilepsy Centre 'Kempenhaeghe', Heeze, The Netherlands

ABSTRACT

Objectives: To evaluate the effects of adjunctive pregabalin 300 mg/day versus placebo on polysomnographic (PSG) variables in patients with well controlled partial seizures and subjectively reported sleep disturbance.

Methods: An exploratory, 4-week, double-blind, randomized study in patients with well controlled partial seizures on AED monotherapy and subjective sleep disturbance over the previous 6 months. Mean changes from baseline to endpoint in PSG and subjective sleep variables (MOS Sleep Scale, Groningen Sleep Questionnaire) in patients on adjunctive pregabalin 300 mg/day (n=8) were compared with patients on placebo (n=7).

Results: Baseline PSGs showed sleep fragmentation. Mean sleep efficiency improved significantly in both treatment groups in the mean baseline to endpoint change there was no significant between-group difference. Pregabalin treatment was associated with a significant reduction in number of awakenings ($p = 0.02$), and improvement in wake time after sleep onset approached significance ($p = 0.055$), suggesting improvement in sleep continuity that was not observed in the placebo group. Pregabalin was also associated with significant improvements in the MOS sleep disturbance and sleep quantity subscales compared with placebo ($p \leq 0.03$). There were no changes in self-reported seizure control.

Conclusions: This exploratory pilot study suggests that pregabalin may improve sleep continuity in patients with clinically relevant sleep disturbance. The effect on disturbed sleep appears independent of seizure control. The effects of pregabalin on disturbed sleep and seizures and their interrelationships warrant further study.

INTRODUCTION

The prevalence of subjectively reported sleep disturbance among people with epilepsy (39%) was found to be significantly greater than among controls (18%), according to a questionnaire-based survey involving responses from 486 patients with partial seizures and 492 age- and gender-matched controls [1]. Furthermore, the presence of sleep disturbance was associated with significant impairment of quality of life, as assessed using SF-36, in both people with epilepsy and in controls. This was an expected finding, since sleep disturbance is known to be associated with impaired quality of life in patients with chronic medical illness [2] and in people who are not chronically ill [3,4]. A novel finding from this previous survey was that the presence of sleep disturbance was associated with significantly greater quality of life impairment than partial epilepsy alone [1]. This highlights the importance of sleep disturbance among people with epilepsy [5-7].

The relationships between epilepsy and sleep disturbance are complex and poorly understood. Previous polysomnographic studies have shown that sleep disturbance in patients with epilepsy is mainly characterized by sleep fragmentation, showing a decreased sleep efficiency and a larger number of awakenings and arousals [5,8-10]. Causes for the reduction in sleep continuity are unknown, but several factors have been implicated. Sleep disorders in epilepsy might be related to associated psychosocial and mood disturbance [11,12], the occurrence of nocturnal or daytime seizures, [11,13] which can alter sleep architecture beyond the postictal phase [5], or due to the presence of epilepsy itself even when seizures are not manifest [8,9]. It has also been demonstrated that AEDs may alter sleep architecture [14,15]. Further complicating the picture is evidence that disturbed sleep can affect seizure control [13]. It has been speculated that AEDs that control seizures and consolidate disturbed sleep might confer benefits to patients beyond seizure control [5].

Pregabalin is a new antiepileptic drug (AED) that is approved in over 60 countries for use in adults for the adjunctive treatment of partial seizures, with or without secondary generalization and the treatment of neuropathic pain. Pregabalin binds to the $\alpha 2\delta$ subunit of voltage-gated calcium channels in the central nervous system and has analgesic, antiepileptic, and anxiolytic activity [16]. Pregabalin does not mimic GABA at $GABA_A$ or $GABA_B$ receptors, nor does it augment $GABA_A$ responses like benzodiazepines or barbiturates [16].

In addition to its efficacy in the treatment of patients with refractory partial seizures [17-20], pregabalin 150-600 mg/day has also been shown to have rapid and potent analgesic efficacy in the treatment of peripheral neuropathic pain [21-23]. In these studies, pregabalin was also associated with a rapid and significant reduction

in sleep disturbance [24]. In healthy volunteers, pregabalin was associated with a significantly higher proportion of slow wave sleep than both placebo and alprazolam [25]. Collectively, these data suggest that pregabalin, while it is not a hypnotic, might benefit disturbed sleep for indications other than pain, such as epilepsy.

The study reported here was a randomized, placebo-controlled exploratory study that employed polysomnography (PSG) and subjective sleep questionnaires to examine the effects of pregabalin 300 mg/day in patients with well controlled partial seizures and self-reported sleep disturbance. The dose of 300 mg/day is in the middle of the 150-600 mg/day therapeutic dose range, and expected to be widely employed in clinical practice.

METHODS

This study was conducted at two sleep centers, both affiliated with the Centre for Human Drug Research in The Netherlands, between December 2002 and June 2004. The study was approved by the central ETHics committee and the local ETHics committees and conducted in accordance with the declaration of Helsinki (South Africa 1996 amendment), Good Clinical Practice and all applicable local laws and regulations. All patients gave written informed consent prior to screening.

Selection of Patients

In total, 17 patients participated in this study. Participants were initially selected from respondents to an earlier survey-based study, investigating the prevalence of sleep disturbance in patients with epilepsy and the impact of sleep disturbance on quality of life [1]. In this cohort of 486 epilepsy patients, 39% had a sleep disturbance, and 35 patients were eligible for recruitment. Many patients from the original pool of patients with sleep disturbance were not eligible to enter this PSG study because they did not fulfil criteria regarding use of antiepileptic medication or because they were treated in a center that only participated in the survey. Only 6 eligible patients entered the study over an 18-month period. Subsequently, advertisements were placed in newspapers, local radio stations, and on websites. This yielded 14 patients for screening in 10 months. Eleven of these patients were entered into the study.

Medical and psychiatric histories were taken by a neurologist. Men or women aged at least 18 years, who were registered outpatients at epilepsy clinics with partial seizures [26] (simple partial, complex partial, or partial seizure with secondary generalization) were allowed

to enter. They were required to have experienced no more than one secondarily generalized tonic-clonic seizure per week over the previous 3 months. Patients were also required to be using monotherapy with carbamazepine (oxcarbazepine included), valproate, or lamotrigine at a dose that was stable for at least 2 weeks.

Only patients with disturbed sleep in the past 6 months, as assessed using the Sleep Diagnosis List (SDL) [27,28] and who had a usual bedtime of between 22: 00 and 01: 00, with 7 to 8.5 hours of time in bed after lights out, were entered. Those taking any concomitant medications with known effects on sleep (except AEDs) were excluded. Patients with SDL-suspected and PSG-confirmed sleep apnea and periodic leg movement (PLM) syndrome were excluded from the study.

Other exclusion criteria such as clinically relevant medical or psychological illness and social conditions that might interfere with normal sleep (e.g. worrying, shift work) were verified during screening. Patients with a history of hypersensitivity or intolerance to pregabalin or GABApentin were also excluded. Women were not pregnant or breastfeeding, and those of childbearing potential were reliably using contraception.

Study Design and Treatment

This was a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. Patients were randomized to either pregabalin 300 mg/day or placebo, both taken in a twice daily (BID) dosing schedule. Pregabalin treatment initiated at 150 mg/d for 4 days, and then increased to 300 mg/day. Randomization was by computer generated code using a 1: 1 ratio. Study center visits were at screening (2–21 days before randomization), the day before treatment (baseline), on the first day of treatment, and then weekly for 4 weeks.

Polysomnography Evaluations

Ambulatory (in-home) polysomnography (PSG) was performed at baseline and at the end of week 4. Patients visited the sleep center and were connected to the Embla recorder for ambulatory polysomnography during nocturnal sleep. The next morning they returned to the sleep center where the electrodes were removed and data were collected.

The data were registered digitally using 4 leads (Fz-Cz, Pz-Oz, C3-A2, C4-A1). An electro-oculogram (EOG) was used to measure the change from wakefulness to superficial sleep (NREM1) and in combination with chin electromyogram (chin EMG) to describe REM sleep. A surface EMG of both tibialis muscles was used to detect periodic leg movements. Oronasal airflow was measured using a

thermistor to detect apneas and hypopneas. Each PSG was manually read by one of the two readers and scored in 30-second epochs using Rechtschaffen-Kales criteria [29]. The polysomnography reports were verified by a neurologist at the sleep center.

The following variables were derived from the PSGs: time in bed (TIB time from 'lights out' to 'get up,' in minutes), total sleep time (TST time occupied by stages 1-4 inclusive and REM, in minutes) sleep efficiency (SE TST divided by TIB, expressed as a percentage) wake time after sleep onset (WASO in minutes) number of awakenings (>15 seconds) arousals (>3 seconds to ≤15 seconds) and the duration of each sleep stage as a percentage of TST. Sleep onset latency (SOLAT) was defined in accordance with clinical practice in the Centre for Sleep & Wake Disorders, as time from 'lights out' to the first epoch of stage 2, in minutes. REM latency was defined as time from SOLAT to the occurrence of the first REM epoch (minutes).

Questionnaire Evaluations

Patients completed a daily seizure diary. The SDL, which evaluated sleep disturbance in the previous 6 months, was completed at screening only. At baseline and at the end of the 4-week treatment period, patients completed the Medical Outcomes Study (MOS) Sleep Scale [30] and the Groningen Sleep Questionnaire (GSQ) [31-33]. The questionnaires have been validated in Dutch.

The SDL, which consists of 75 randomly distributed questions about 6 common sleep disturbances (insomnia, sleep apnea, periodic leg movements, daytime sleepiness, narcolepsy, psychiatric sleep disturbance) in the past 6 months, was answered on a 5-point scale from 1=never to 5=very often or always. A total mean score ≥3 in a category indicated the presence of a sleep disturbance. The MOS-Sleep Scale evaluated sleep in the past 4 weeks and included 12 questions about sleep, answered on a 6-point scale from 1=all of the time to 6=none of the time, as well as perceived duration of sleep and sleep latency. This scale has been found a reliable and valid tool for the subjective assessment of sleep [34]. The GSQ included 14 questions about sleep the previous night, answered Yes or No. Total scores range from 0 to 14, with a higher score indicating better subjective quality of sleep. This questionnaire has been validated in depressed patients [31] and has been used in studies in other populations [32,33].

Tolerability and Safety

All spontaneously reported or observed adverse events were recorded in a diary and reported at weekly clinic visits. Routine laboratory

tests (haematology, blood chemistry [including liver enzymes and electrolytes]) were conducted at screening baseline and at week 4.

Statistical Analysis

As this was an exploratory study, no power calculations were made. The principal efficacy variable was the comparison of the mean change in sleep efficiency from baseline to week 4 between the pregabalin group and the placebo group. Only patients with a baseline PSG and week 4 PSG were included in the analysis. Analysis of within group changes from baseline in sleep efficiency was a secondary efficacy variable. Analysis of within-group and between-group changes in all other PSG variables and questionnaire-based assessments were also secondary.

Between-group differences were derived from the ancova model, which included treatment as a factor and adjustment for baseline. Within-group differences were determined using an ANOVA model with treatment as a factor.

RESULTS

Patient Characteristics and Disposition

Seventeen eligible patients entered the study. The baseline demographic characteristics (Table 1) and seizure types (Table 2) were similar in the placebo and pregabalin groups. Epilepsy was due to structural lesions in 3 patients. The ETiology was unknown in the other patients (2 of whom had a family history of epilepsy). Subjects were clinically seizure free during the 1-3 week period between screening and the first PSG. The most common sleep complaint on the SDL was compatible with primary insomnia. Three patients scored positive on the subscales for 'psychiatric sleep disorder' as well as for 'primary sleep disorder,' but further psychiatric examination provided no clinical indications for psychological distress or psychiatric disease that warranted exclusion. The apnea-hypopnea index (AHI) on the baseline PSG ranged from 0 to 2.1, and periodic leg movement index (PLMI) ranged from 0 to 7.6 across all patients.

One patient discontinued pregabalin treatment on day 12 due to increased seizure frequency. Another patient completed the study, but data of the second PSG were lost due to technical problems. Therefore, one patient from each group was not included in the analyses of sleep variables.

Seizure Frequency

During the 4-week treatment period 2 patients in the placebo group and 3 in the pregabalin group experienced seizures. All these patients in these 'per protocol' groups first reported seizures in their diaries between Days 1 and 5 of treatment, but none of them showed a clear exacerbation compared to the pre-study period. No clinical seizures were reported during baseline PSG or at week 4 PSG, but the EEG montage was too limited to exclude subclinical or interictal activity during the night. No new seizure types emerged in any patient. Concomitant AED medications were not changed during the study.

PSG Variables

The principal efficacy variable, mean sleep efficiency, improved in both treatment groups (Table 3). The difference between the pregabalin group and the placebo group was not statistically significant. The difference between the pregabalin and placebo groups in the mean change in the number of awakenings was statistically significant (95% CI: 0.1 to 7.6 $p = 0.02$) and the difference in WASO approached statistical significance (95% CI: -1.0 to 78.9 $p = 0.055$). In the pregabalin group, significant within-group reductions from baseline in the mean number of awakenings and WASO were observed, as opposed to nonsignificant increases in the placebo group. In the within-group comparison, placebo treatment was associated with a significant decrease in SOLAT (from 38.1 to 12.9 minutes), compared with no change in the pregabalin group no statistically significant difference was seen in the between group comparison. No significant within-group or between-group differences were observed in the number of arousals or the percentages of sleep stages.

Sleep Questionnaires

Mean GSQ scores, which rates sleep of the previous night, improved significantly between baseline and week 4 in the pregabalin group but not in the placebo group (Table 4). The difference between groups in the mean change of this score also reached statistical significance (95% CI: -9.0 to -0.7 $p = 0.03$). Data are presented for 6 of 8 MOS sleep subscales snoring and awakening short of breath are not presented because patients with sleep apnea were excluded. Improvements were observed within the pregabalin group across most MOS subscales, and were statistically significant for 4 of the 8 subscales (Table 4). In the placebo group, changes from baseline to week 4 were modest and did not reach statistical significance. The difference in the mean

change from baseline between the pregabalin and placebo groups was statistically significant for 2 subscales sleep disturbance and sleep quantity.

Tolerability and Safety

Mild to moderate treatment-emergent adverse events were reported in all patients in both treatment groups. Headache was the most frequent adverse event, occurring in 6 patients in the placebo group and three in the pregabalin group. Other adverse events occurring in 2 or more patients in either treatment group included the following: dizziness in 4 patients on pregabalin, somnolence in 2 patients in each group, and asthenia in 1 placebo- and 2 pregabalin-treated patients. No serious adverse events were reported.

DISCUSSION

The aim of this study was to explore the effects of the antiepileptic drug pregabalin on sleep disturbance in patients with well-controlled partial seizures and subjective sleep disturbance. Subjectively reported sleep disturbance was based on the SDL, which evaluated sleep in the previous 6 months. The characteristics were compatible with primary insomnia. Two other questionnaires, the GSQ (previous night) and MOS subscales (previous month), also indicated the presence of sleep disturbance [34,35]. The PSG evaluation seemed to corroborate this. Baseline PSGs indicated that patients had sleep fragmentation as indicated by sleep efficiency, WASO, and number of awakenings when compared with normal sleep variables reported in other studies [36-38].

The results suggest that pregabalin 300 mg/day may have a positive effect on disturbed sleep based on subjective assessments (questionnaires), but PSG findings were not as consistent. Definitive conclusions are precluded by the small numbers of patients and the changes observed in the placebo group. There was no significant difference between the pregabalin and placebo groups in the mean change from baseline and at 4 weeks in the primary efficacy variable, sleep efficiency. However, pregabalin was associated with a significant improvement in the number of awakenings compared with placebo. Despite the lack of statistical power, the mean reduction in the number of awakenings in the pregabalin group was substantial as was the mean WASO score, which decreased from 51 min to 15 min. These improvements suggest that pregabalin might consolidate sleep in patients with sleep disturbance that is characterized by sleep fragmentation. The mean MOS sleep quantity score increased

significantly with pregabalin treatment compared to placebo (mean placebo – pregabalin difference 1.5 hour, 95% CI: 0.4 to 2.7) in addition to a significant improvement in the MOS sleep disturbance scale (mean placebo – pregabalin difference 16.9, 95% CI: 1.3 to 32.5). The magnitude of improvement in subjective sleep variables appeared greater than the improvement observed in objective (PSG) assessments. This discrepancy seems to indicate that relatively small improvements in sleep continuity might be perceived as a relief to the patient. However, larger studies are needed to further examine the relationship between objectively measured and subjectively reported sleep effects.

Although there are several other studies in which the effects of AEDs on sleep have been evaluated, subjective effects on sleep disturbance are rarely reported. It is difficult to compare our findings with the results of these studies, due to wide differences in patient population, seizure frequency, duration of treatment and methodology. The effects of AEDs on sleep have been summarized in different publications [14,15,39], which report contradictory results on different stages of sleep, even within the same studies.

Pregabalin is an antiepileptic drug, and epilepsy-related sleep disorder may be partly related to subclinical nocturnal seizure manifestations, leading to fragmentation of the sleeping pattern by nocturnal seizure activity [40]. Although these have not been recorded by the PSGs, undetected seizure improvement is unlikely to be the only explanation for pregabalin-induced sleep improvement. Pregabalin has also been observed to increase slow wave sleep in healthy volunteers [25] and to improve sleep disturbance in chronic pain states [21-24,41]. The results of this study could have been affected by factors such as seizure type or localization, concomitant AED type or (unnoticed) intercurrent seizures. However, while no changes in these potential confounds were observed during the study, the study was too small to exclude the influence of covariates on the effects of treatment.

Larger studies are warranted to clarify the relevance of the finding of this exploratory study. Such studies could be more challenging than would be expected from the frequency and the impact of sleep problems in epilepsy [1]. Recruitment for this study was surprisingly difficult, which was unexpected, since the study was performed in conjunction with 2 major epilepsy centers and 2 large teaching hospitals with traditions in clinical research. It seems that the problem is much more important for patients themselves than physicians, as patient-directed advertising recruited more patients more quickly than the study centers.

To our knowledge, this study is the first randomized, double-blind, placebo-controlled study in which the impact of an AED is specifically examined in a sleep disturbed subgroup. The results

of this exploratory study suggest that pregabalin 300 mg/day may improve sleep continuity and subjective sleep quality in these epilepsy patients and that this seems independent of seizure control. The effects of pregabalin on disturbed sleep and seizures and their interrelationships warrant further study.

Table 1 Baseline characteristics

	Placebo (n=8)[a]	Pregabalin (n=9)[a]
Demographics		
Women/men (# of patients)	3/5	2/7
Mean age (range), yr	45.9 (19-67)	38.3 (24-51)
Mean BMI (SD), kg/m^2	27.9 (5.4)	25.2 (4.7)
Concomitant AED (# of patients)		
Carbamazepine	1	5
Oxcarbazepine	1	1
Valproate	3	3
Lamotrigine	3	0
Baseline SDL ≥ 3[b] (# of patients)		
Insomnia	7	5
Narcolepsy	0	0
Periodic limb movements	0	2
Excessive daytime sleepiness	1	3
Psychiatric sleep disorder	2	1

a 1 patient from each the pregabalin and placebo groups did not have baseline and week 4 PSGs and therefore are not included in the analysis of sleep variables; b Only patients with a score ≥3 on one of the SDL subscales were included in the study. Patients with sleep apnea based on SDL or PSG were excluded from the analysis of sleep variables. Some patients had a score ≥3 on more than one SDL subscale.

Table 2 History of seizure types

	Placebo (n=8)[a]	Pregabalin (n=9)[a]
Partial seizures		
Simple partial seizures	6	7
Complex partial seizures	5	6
Partial seizures evolving to secondarily generalized seizures	2	4
Secondarily generalized seizures		
Clonic seizures	2	1
Tonic seizures	1	2
Tonic-clonic seizures	3	3

a Some patients experienced more than one seizure type

Table 3 Mean (SD) baseline and week 4 PSG variables

	Placebo (n=7)			Pregabalin (n=8)			Pregabalin vs. placebo			
	Baseline	Week 4	P value [a]	Baseline	Week 4	P value [a]	placebo - pregabalin	95% CI		P value [b]
TIB, min	466 (49)	468 (68)	0.97	536 (55)	510 (73)	0.25	25.3	-46.3,	96.9	0.46
TST, min	352 (93)	386 (55)	0.40	431 (77)	447 (98)	0.23	-7.0	-80.7,	66.7	0.84
Sleep efficiency, %	75.6 (18.7)	83.2 (11.3)	0.02	80.6 (13.6)	87.1 (8.9)	0.004	-1.32	-8.3,	5.6	0.69
SOLAT, min	38.1 (35.2)	12.9 (7.8)	0.01	24.3 (22.9)	22.6 (19.3)	0.2	-11	-29.2,	7.6	0.23
No. of awakenings [c]	4.6 (2.6)	5.4 (3.5)	0.57	6.0 (4.6)	2.8 (5.1)	0.02	3.9	0.1,	7.6	0.04
WASO, min	53.9 (34.3)	55.3 (43.6)	0.85	50.5 (41.6)	15.1 (29.5)	0.01	39	-1.0,	78.9	0.06
No. of arousals [c]	6.5 (3.9)	5.8 (2.3)	0.61	3.8 (2.5)	3.0 (2.6)	0.15	2.4	-1.4,	6.1	0.19
REM latency, min	123.3 (65.1)	80.6 (34.3)	0.10	90.8 (44.0)	75.9 (39.8)	0.06	2.7	-43.1,	48.5	0.90
REM, %	17.6 (8.0)	17.9 (5.6)	0.75	20.8 (3.9)	21.2 (5.9)	0.52	-1.9	-7.8,	4.1	0.51
Stage 1%	8.7 (5.3)	7.6 (4.5)	0.57	9.1 (6.2)	6.4 (8.2)	0.18	1.5	-4.4,	7.3	0.59
Stage 2, %	58.5 (6.9)	61.6 (10.5)	0.25	57.5 (8.0)	58.9 (7.8)	0.60	1.9	-6.0,	9.7	0.61
Stage 3+4, %	15.2 (13.6)	12.9 (12.9)	0.31	12.7 (8.2)	13.5 (8.9)	0.72	-2.7	8.6,	3.1	0.33

a P value for within group change based on ANCOVA that included treatment effect and adjustment for baseline score; b P value based on comparison of LS mean change from baseline at week 4 between pregabalin and placebo groups; c Sleep continuity was visually scored on the PSG. Arousal is defined by the ASDA-criteria: a sudden shift of EEG to alpha, theta or beta >16 Hz (no sigma) with duration of >3 - ≤15 seconds, preceded by ≥10 sec of sleep. Arousals= number of arousals/hour. Awakening is a sudden shift of EEG to alpha, theta or beta >16 Hz (no sigma) with a duration of > 15 seconds / or an entire epoch of alpha activity. Awakenings and arousals are shown in number per whole night.

Table 4 Mean (SD) baseline and week 4 sleep questionnaire-based variables.

	Placebo (n=7)			Pregabalin (n=8)			Pregabalin vs. placebo			
	Baseline	Week 4	P value[a]	Baseline	Week 4	P value [a]	placebo - pregabalin	95% CI		P value [b]
GSQ [c]	6.3 (3.7)	6.6 (4.2)	0.93	7.3 (2.9)	11.6 (2.4)	0.005	-4.8	-9.0,	-0.7	0.03
MOS										
Sleep disturbance	57.0 (28.9)	44.5 (30.2)	0.053	48.2 (15.5)	20.0 (10.6)	0.002	17.6	0.8,	34.4	0.04
Sleep quantity [d]	5.9 (1.7)	5.4 (1.5)	0.11	6.9 (1.4)	7.6 (1.0)	0.03	-1.3	-2.7,	-0.4	0.01
Sleep adequacy [d]	34.3 (36.5)	31.4 (37.6)	0.52	51.4 (33.9)	67.1 (24.3)	0.07	-26	-57.0,	5.2	0.09
Somnolence	47.6 (28.4)	31.4 (23.6)	0.09	33.3 (26.1)	37.1 (20.0)	0.97	-13	-34.6,	8.8	0.22
Overall sleep problems index (6 items) [e]	44.4 (22.5)	41.7 (22.9)	0.84	33.7 (13.8)	22.6 (10.7)	0.03	11.7	-4.4,	27.9	0.14
Overall sleep problems index (9 items) [e]	52.9 (22.2)	46.4 (24.6)	0.43	43.0 (16.4)	27.6 (11.8)	0.01	12.4	-6.2,	30.9	0.17

a P value for within group change based on ANCOVA that included treatment effect and adjustment for baseline score; b P value based on comparison of LS mean change from baseline at week 4 between pregabalin and placebo groups; c GSQ possible score range 0-14. Higher score = better sleep; d Higher score = better sleep; e MOS overall sleep problems indices include questions regarding sleep latency, sleep disturbance, adequacy and somnolence

REFERENCES

1 de Weerd A, de Haas S, Otte A, Trenite DK, van Erp G, Cohen A, de Kam M, van Gerven J. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia 2004 45: 1397-1404.

2 Manocchia M, Keller S, Ware JE. Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. Qual Life Res 2001 10: 331-345.

3 Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep 1999 22 Suppl 2: S379-S385.

4 Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. sf-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. Psychosom Med 2001 63: 49-55.

5 Bazil CW. Epilepsy and sleep disturbance. Epilepsy Behav 2003 4 Suppl 2: S39-S45.

6 Vaughn BV, D'Cruz OF. Sleep and epilepsy. Semin Neurol 2004 24: 301-313.

7 Manni R, Tartara A. Evaluation of sleepiness in epilepsy. Clin Neurophysiol 2000 111 Suppl 2: S111-S114.

8 Besset A. Influence of generalized seizures on sleep organization.In: Sleep and epilepsy eds Sterman MB, Shouse MN, Passouant P, New York: Academic press, 1982: 339-346.

9 Touchon J, Baldy-Moulinier M, Billiard M, Besset A, Cadilhac J. Sleep organization and epilepsy. Epilepsy Res Suppl 1991 2: 73-81.

10 Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia 1998 39: 150-157.

11 Harden CL. The co-morbidity of depression and epilepsy - Epidemiology, etiology, and treatment. Neurology 2002 59: S48-S55.

12 Vaughn BV. Differential diagnosis of paroxysmal nocturnal events in adults.In: Sleep and Epilepsy: the Clinical Spectrum eds Bazil CW, Malow BA, Sammaritano M, Amsterdam: Elsevier Science B.V., 2002: 325-338.

13 Bazil CW. Sleep and epilepsy. Curr Opin Neurol 2000 13: 171-175.

14 Sammaritano M, Sherwin A. Effect of anticonvulsants on sleep. Neurology 2000 54: S16-S24.

15 Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med 2003 4: 51-55.

16 Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: The calcium channel alpha(2)-delta (alpha(2)-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007 73: 137-150.

17 French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. Neurology 2003 60: 1631-1637.

18 Arroyo S, Anhut H, Kugler AR, Lee CM, Knapp LE, Garofalo EA, Messmer S. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 2004 45: 20-27.

19 Brodie MJ. Pregabalin as adjunctive therapy for partial seizures. Epilepsia 2004 45 Suppl 6: 19-27.

20 Beydoun A, Uthman BM, Kugler AR, Greiner MJ, Knapp LE, Garofalo EA. Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy. Neurology 2005 64: 475-480.

21 Dworkin RH, Corbin AE, Young JP, Jr., Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003 60: 1274-1283.

22 Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004 110: 628-638.

23 Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, Versavel M. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004 109: 26-35.

24 Jaffe M, Iacobelis D, Young JPeal. Post-hoc results show beneficial effects of pregabalin in patients with osteoarthritis of the hip. Poster presented at American College of Rheumatology, in Philadelphia, Pennsylvania, usa, October 28-November 2 2000.

25 Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005 28: 187-193.

26 Bancaud J, Henriksen O, Rubiodonnadieu F, Seino M, Dreifuss FE, Penry JK. Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures. Epilepsia 1981 22: 489-501.

27 Sweere Y, Kerkhof GA, De Weerd AW, Kamphuisen HA, Kemp B, Schimsheimer RJ.

The Sleep Diagnosis List (SDL): a questionnaire for screening general sleep disorders. Sleep-Wake Research in the Netherlands 1998 9: 117-121.
28 Sweere Y, Kerkhof GA, De Weerd AW, Kamphuisen HA, Kemp B, Schimsheimer RJ. The validity of the Dutch Sleep Disorders Questionnaire (sdq). J Psychosom Res 1998 45: 549-555.
29 Rechtschaffen A, Kales A. A manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects. US Department of Health, Education, and Welfare, Public Health Service, Washington DC US Governmoent Printing Office 1968.
30 Hays R.D. and Stewart A.L. Sleep Measures. In: Measuring Functioning and Well-Being, edited by Stewart AL, Ware Jr JE. Durham: Duke University Press . 1992.
31 Mulder-Hajonides van der Meulen, W. R. E. H., Wijnberg, J. R., Hollander, J. J., de Diana, L. P. F., and van den Hoofdakker, R. H. Measurement of subjective sleep quality. Eur Sleep Res Soc Abstr (5), 98. 1980.
32 Meijman T, Thunnissen M, de Vries-Griever A. The after-effects of a prolonged period of day-sleep on subjective sleep quality. Work Stress 1990 4: 65-70.
33 Verhelst MMR, Kerkhof GA, Schimsheimer RJ, Kemp B, Weerd. Objective sleep quality versus subjective sleep quality in 332 patients. J Sleep Res 2000 9: 200.
34 Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med 2005 6: 41-44.
35 Leppamaki S, Meesters Y, Haukka J, Lonnqvist J, Partonen T. Effect of simulated dawn on quality of sleep--a community-based trial. BMC Psychiatry 2003 3: 14.
36 Buysse DJ, Monk TH, Carrier J, Begley A. Circadian patterns of sleep, sleepiness, and performance in older and younger adults. Sleep 2005 28: 1365-1376.
37 Cicolin A, Magliola U, Giordano A, Terreni A, Bucca C, Mutani R. Effects of levetiracetam on nocturnal sleep and daytime vigilance in healthy volunteers. Epilepsia 2006 47: 82-85.
38 Goel N, Kim H, Lao RP. Gender differences in polysomnographic sleep in young healthy sleepers. Chronobiol Int 2005 22: 905-915.
39 Placidi F, Scalise A, Marciani MG, Romigi A, Diomedi M, Gigli GL. Effect of antiepileptic drugs on sleep. Clin Neurophysiol 2000 111 Suppl 2: S115-S119.
40 Manni R, Galimberti CA, Sartori I, Politini L, Murelli R, Tartara A. Nocturnal partial seizures and arousals/awakenings from sleep: an ambulatory EEG study. Funct Neurol 1997 12: 107-111.
41 Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP, Jr., LaMoreaux LK, Martin SA, Sharma U. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005 52: 1264-1273