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Treatment Effects of Gabapentin for Primary Insomnia

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Objectives: The prevalence of insomnia is very high in our society. Although pharmacological treatment of insomnia is available, most hypnotics have been shown to alter sleep architecture and have many adverse effects. Gabapentin was originally designed for antiepileptic therapy; however, some studies reported that its use increases slow-wave sleep in healthy volunteers or patients. Our goal was to evaluate the benefits of gabapentin in the treatment of primary insomnia in patients. **Methods:** Eighteen patients with primary insomnia participated in the study. They received gabapentin treatment for at least 4 weeks. All patients received polysomnography, a biochemical blood test, and neuropsychological tests before and after the treatment period. All measures were analyzed with Student *t* test to examine the treatment effects of gabapentin, except that the measures of heart rate variability were analyzed with analysis of variance.

Results: Polysomnographic study revealed increased sleep efficiency and slow-wave sleep, decreased wake after sleep onset, and spontaneous arousal index after gabapentin treatment. The biochemical blood test revealed decreased prolactin levels in the morning after treatment. Electroencephalographic power spectral analysis showed increased delta-2 and theta power in sleep stage 1 and decreased sigma activity power in sleep stages N2 and N3 after gabapentin treatment. Heart rate variability analyses also showed a significant increase in normalized high frequency percentage in sleep stages N2 and N3 and low frequency-high frequency ratio in sleep stage N2 after treatment. In addition, neuropsychological tests revealed the elevation of visual motor processing speed after gabapentin treatment.

Conclusions: Gabapentin enhances slow-wave sleep in patients with primary insomnia. It also improves sleep quality by elevating sleep efficiency and decreasing spontaneous arousal. The results suggest that gabapentin may be beneficial in the treatment of primary insomnia.

Key Words: gabapentin, insomnia, polysomnography, heart rate variability, EEG spectral analysis

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Benzodiazepines have been used to treat insomnia for many years. However, they have been known to decrease slow-wave sleep, have many adverse effects, and have addictive

properties. The newest hypnotics, benzodiazepine receptor agonists, are better than benzodiazepine hypnotics in altering sleep architecture. However, the many adverse effects, including tolerance, dependence, abuse, delirium, nightmares and hallucinations, and loss of memory have also been reported.^{1–4} Better treatment of chronic insomnia is still pending.

Gabapentin was approved for treatment of partial seizures by the Food and Drug Administration in 1993. Its precise pharmacological mechanism in humans remains unknown. Even so, gabapentin's applicable uses have since expanded. It has been approved for the treatment of neuropathic pain^{5–8} and restless leg syndrome^{9–12} in addition to its original purpose as an anti-convulsant medication. Owing to its strong safety record and limited adverse effects,¹³ such as somnolence, numerous off-label uses have also been extended for various clinical trials. As early as 1988, gabapentin was shown to augment whole-blood serotonin in healthy young men, and its increase in peripheral serotonin points was considered paradigmatically to an increase in the bioavailability of serotonin that accounts for the increase¹⁴ in sleep stages 3 and 4. Recently, a report indicated that there is a direct correlation between gabapentin and increased slow-wave sleep in healthy adults,¹⁵ and a separate case report demonstrated the successful application of gabapentin in treating chronic insomnia.¹⁶ As pointed out by fellow researchers, the patent for gabapentin has already expired, and it may not produce strong enough results financially to warrant a large-scale double-blind clinical trial for its application in sleep medicine sponsored by the pharmaceutical industry. However, we think that gabapentin is a potentially effective treatment of chronic insomnia. The goal of this study was to evaluate the efficacy of gabapentin treatment in sleep and daytime functionality in patients with primary insomnia.

MATERIALS AND METHODS

Subjects and Methods

Eighteen patients with primary insomnia were recruited from a sleep disorder clinic in a central Taiwan medical center. The study group was composed of eleven females and 7 males, with a mean (SD) age of 43.2 (15.4) years; their mean body mass index was 22.77 (2.59) kg/m². All participants signed an informed consent that was approved by the institutional review board of the medical center. An overnight polysomnographic (PSG) study was conducted for the screening of any other sleep disorders. The inclusion criteria were (1) subjective complaints of difficulty initiating sleep and/or difficulty maintaining sleep for more than 3 months, (2) no prior history of or current psychiatric disorder other than insomnia by clinical interview, (3) no prior history of or current major medical disorders by clinical interview, (4) no prior history of or current other sleep disorders as diagnosed by clinical interview, and (5) PSG findings of apnea-hypopnea index less than 15 and no other primary sleep disorders, such as periodic limb movement disorder or parasomnia and other primary sleep disorders.

The study was an open-label clinical trial. All subjects went through a series of examinations before and after gabapentin treatment, including PSG, electroencephalographic (EEG) power

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spectral and heart rate variability (HRV) analyses, biochemical blood and neuropsychological tests, and subjective ratings of sleep quality on the Pittsburgh Sleep Quality Index (PSQI).

Gabapentin Titration and Treatment Phase

The dose of gabapentin treatment was given by following a titration procedure, starting with a lowest dose of 100 mg per night. Patients were instructed to take the medication right after supper and/or at bedtime because the medicine has an adverse effect of somnolence and the peak serum level is reached in 2 to 3 hours (T_{max}) with an absolute bioavailability of 60% after oral administration.¹⁷ The dose was gradually increased depending on the patient's tolerance and satisfaction with his/her sleep. Once the patients reported satisfactory feeling in sleep and showed improvement on the PSQI, the treatment doses were fixed and were given continuously for the next 4 weeks, and then the study was concluded.

Biochemical Blood Tests

The uric acid, high-sensitive C-reactive protein, cortisol, ferritin, serum iron, human growth hormone, and prolactin levels were tested before and after the gabapentin treatment in every patient. All of these biochemical blood tests were for the evaluation of systemic response to gabapentin treatment.

Polysomnographic Recording

Subjects underwent overnight PSG recording using Rembrandt PSG equipment and software (Medcare, Reykjavik, Iceland) in the sleep laboratory. The PSG was recorded and scored according to *The AASM Manual for the Scoring of Sleep and Associated Events* by the American Academy of Sleep Medicine.¹⁸ Electroencephalogram was recorded from O1, O2, C3, and C4 with reference lead on A1 and A2 of the opposite side. Electrooculogram was recorded from E1-M2 (E1 is placed 1 cm below the left outer canthus) and E2-M2 (E2 is placed 1 cm above the right outer canthus). Chin electromyogram was recorded from electrodes of one in the midline 1 cm above the inferior edge of the mandible and one 2 cm below the inferior edge of the mandible and 2 cm to the right/left of the midline. The surface electromyogram of the right and left anterior tibialis muscles was recorded and scored to quantify periodic leg movements in sleep using a standard criterion defined by a task force from the American Academy of Sleep Medicine¹⁶ and the International Restless Legs Syndrome Study Group.¹⁹ Electrocardiogram (ECG) was recorded from a standard D2 lead. Standard recordings of oral and nasal airflow, thoracic and abdominal movements, and oximetry were performed to detect apneas or hypopneas.

Power Spectral Analysis of EEG Activities

Electroencephalographic activities from C3-A2 or C4-A1 leads in the PSG were analyzed for EEG spectrum power. The spectrum of EEG activities were divided into the following rhythmic bands: delta-1 (0.5–1.5 Hz), delta-2 (1.5–3.0 Hz), theta (3.0–8.0 Hz), alpha (8.0–12 Hz), sigma (12–14 Hz), beta-1 (14–20 Hz), beta-2 (20–32 Hz), and gamma (32–64 Hz). The EEG was recorded with a sampling rate of 256 Hz and was computed by a fast Fourier transform routine for a window of 4 seconds giving 0.25Hz frequency resolution. Both absolute power and percentage against total power were calculated for data analyses.²⁰

Heart Rate Variability

The ECG was recorded at a sampling rate of 400 Hz, chosen for maximum precision in measuring the R-R interval data. The QRS complexes were automatically detected using an automated algorithm, and the time interval between 2 R waves top were calculated to allow the computation of the R-R interval time series. All of the HRV was analyzed during the 10 minutes' segment of various sleep stages including stages N1, N2, N3, and rapid eye movement (REM). Wake after sleep onset (WASO) and movement area were excluded. Power spectral analysis was performed on the R-R interval as HRV according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.²¹ The low-frequency (LF) power covered the frequency range of 0.04 to 0.15 Hz, and the high-frequency (HF) power covered the frequency range of 0.15 to 0.4 Hz.

Pittsburgh Sleep Quality Index

The PSQI was administered to patients with poor sleep as a screening test, for the evaluation of subjective sleep quality, latency, and duration; habitual sleep efficiency; sleep disturbances; use of sleeping medication; and daytime dysfunction.²² It was given to every patient before the gabapentin treatment and then readministered whenever they felt their sleep had improved after the titration of the medicine. Therefore, it may be administered more than twice during the study. The ratings on the PSQI were used to determine the gabapentin dose during the dose titration for the study.

Neuropsychological Tests

Neuropsychological tests for cognitive ability were administered on every patient before and after the gabapentin treatment. These included the digit symbol subtest of the Wechsler Adult Intelligence Scale III (WAIS-III),^{23,24} the logic memory test of the Wechsler Memory Scale III (WMS-III),^{25,26} and the Stroop test on color naming.^{27,28} They were administered to evaluate the effects of gabapentin treatment on cognitive functioning during daytime hours. The digit symbol subtest tested

TABLE 1. Polysomnographic Findings Before and After Gabapentin Treatment

Treatment	Sleep															
	Sleep Period		Efficiency, %		Sleep Onset		REM Onset		WASO		Stage N1		Stage N2		Stage N3	
	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx
Mean	351.56	340.72	80.00	87.17	17.58	14.58	132.94	114.42	16.45	7.84	6.22	5.31	55.25	52.57	10.47	17.68
SD	46.31	29.16	14.79	11.37	15.07	13.61	107.34	38.38	14.78	9.92	4.21	4.04	14.41	9.79	9.86	9.88
<i>t</i>		0.4226		0.0335		0.5378		0.4498		0.0101		0.4318		0.4791		0.0007

t test was performed between the results before and after gabapentin treatment.

Rx indicates treatment.

visual motor coordination in the patients, and the logic memory test determined immediate and delayed memory and memory retention; the Stroop test was to examine the inhibitory ability of executive functions.

Statistical Analysis

The Student *t* test was performed to examine the difference between measures before and after gabapentin treatment for biochemical blood tests, EEG power spectral analysis, PSG architecture parameters, PSQI, and higher-cortical function tests. The blood tests were composed of tests for uric acid, high-sensitive C-reactive protein, cortisol, growth hormone, and prolactin levels. In addition, a 2-by-4 two-way analysis of variance was conducted for the comparisons of changes in HRV measures after treatment among the 4 sleep stages (N1, N2, N3, and REM). Whenever there was a significant interaction, post hoc comparisons were conducted using *t* test with Bonferroni correction. The SPSS-14 edition (SPSS Inc, Chicago, Ill) was used for the statistical analyses.

RESULTS

Titration and Treatment Doses of Gabapentin After Titration

It took 3 to 5 weeks to complete the titration. A fairly small starting dose (100 mg) was used and was gradually increased to make the adaptation easier for the patients. The required treatment doses were 200 mg in 1 patient, 300 mg in 4 patients, 400 mg in 1 patient, 600 mg in 10 patients, and 900 mg in 2 patients. The doses ranged from 200 to 900 mg; the dose for most patients was 600 mg, and the mean dose was 540 mg.

Polysomnographic Examination

The PSG recordings revealed significant improvement of sleep between before and after gabapentin treatment (Table 1). The gabapentin treatment improved sleep efficiency from 80.00% to 87.17% (*t* = -2.31, *P* < 0.05), decreased WASO from 16.45% to 7.84% (*t* = 2.90, *P* < 0.05), and increased sleep stage N3 percentage from 10.47% to 17.68% (*t* = -4.11, *P* < 0.005) and decreased spontaneous arousal index from 24.71 to 15.72 per hour (*t* = 2.55, *P* < 0.05). Sleep onset latency, however, did not show a significant change (from 17.58–14.58 minutes; *t* = 0.63, not significant), and the percentage of REM sleep (from 13.48%–15.57%; *t* = -1.41, not significant) did not show significant changes either.

Electroencephalographic Power Spectrum

When comparing the power spectrum data before and after the gabapentin treatment, it was revealed that there was an elevation of delta-2 and theta activity power in sleep stage N1

(*t* = -3.37, *P* < 0.005 and *t* = -2.67, *P* < 0.05, respectively) on both activities after the treatment and that there was a decrease of sigma activity power in sleep stages N2 and N3 (*t* = 2.45, *P* < 0.05 and *t* = 2.23, *P* < 0.05, respectively) after the treatment (Table 2). The rest of the frequency bands did not show a significant change after the treatment.

Biochemical Blood Tests

By comparing the results of the blood tests performed before and after the treatment with gabapentin, it was noted that the prolactin level in the morning significantly decreased from 12.52 (8.32) to 9.15 (6.86) after the gabapentin treatment (*t* = 3.003, *P* < 0.01). The growth hormone and cortisol levels, however, did not change significantly after the treatment.

Heart Rate Variability

Five minutes of continuous stable ECG recording is required for the standard HRV analysis.²¹ Some subjects, however, did not generate stable segment of recording that is long enough for HRV analysis in some sleep stages, especially in N1 and N3 sleep stages. Thus, instead of using individual data, the data derived from all valid segments of recordings were inputted for statistical analyses. The results showed significant interaction effects for normalized LF% (nuLF%), nuHF%, and nuLF/nuHF ratio of stage N3 (Fs = 26.88, 26.88, and 23.10, respectively; *P* < 0.005). Post hoc comparisons comparing the measures before and after treatment showed a significant increase of nuHF% of stage N3 from 45.36% to 78.79% (*t* = 6.49; *P* < 0.001) and a significant decrease of the ratio of nuLF/nuHF from 2.12 to 0.39 in stage N3 (*t* = 6.49; *P* < 0.001). Table 3 shows the data of the other HRV measures.

Pittsburgh Sleep Quality Index

Because the gabapentin doses were increased very slowly and patients were followed up closely, the second PSQI was performed only after subjective reports of definite improvement in sleep quality; therefore, only 2 to 3 PSQIs were needed for confirmation of improvement in sleep to reach the gabapentin optimal dose. When the PSQI result was compared before and after gabapentin titration, it showed a remarkable and significant decrease of the global score from 13.54 to 7.67 with *t* = 4.17 and *P* < 0.001. That there was a significant before-and-after difference in score indicates that the titration of gabapentin qualifies as the proper dose in each studied patient.

Neuropsychological Tests

The results of cognitive tests revealed significant improvements in the digit symbol and logic memory tests after the gabapentin treatment. The score on the digit symbol test of WAIS-III and of the immediate, delay, and retention memory indices of WMS-III all improved after treatment (Table 4). The

Stage REM		Obstructive Apnea		Central Apnea		Hypopnea		Respiratory Disturbance Index		Spontaneous Arousal		Periodic Limb Movement Index		Minimum O ₂	
Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx
13.48	15.57	0.00	8.61	0.56	1.44	33.28	44.39	6.88	11.17	24.71	15.72	0.30	0.51	88.78	86.67
6.51	4.70	0.00	27.38	1.29	2.33	25.25	36.51	4.72	9.38	13.84	11.10	1.01	1.90	4.37	4.75
	0.1777		0.1999		0.2090		0.2493		0.0555		0.0208		0.7007		0.0511

TABLE 2. Spectral Power of EEG Activities in Different Sleep Stages Before and After Gabapentin Treatment

Stage	Delta, $\mu\text{V}^2/\text{Hz}$		Delta-1 (0.5–1.5 Hz)		Delta-2 (1.5–3.0 Hz)		Theta (3–8.0 Hz)		Alpha (8.0–12 Hz)		Sigma (12–14 Hz)		Beta-1 (14–20 Hz)		Beta-2 (20–32 Hz)		Gamma (32–64 Hz)	
	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx
N1	18,122	19,473	34,213	35,927	2031	3017*	675	943*	573	610	232	234	161	138	68	54	9	9
N2	25,491	29,936	45,530	53,859	5452	6013	1229	1505	608	584	521	405*	181	139	38	36	8	13
N3	59,455	65,939	103,973	116,166	14,937	15,712	1869	2264	537	518	427	310*	135	88	24	21	6	3
REM	11,523	10,713	21,322	19,535	1724	1892	574	628	270	268	136	116	112	82	50	38	4	4

* $P < 0.05$ in t test.

TABLE 3. HRV in Various Sleep Stage Before and After the Gabapentin Treatment

Stage	VLf, ms^2		Lf, ms^2		HF, ms^2		Total Power		nuLF%		nuHF%		nuLF/nuHF	
	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx	Before Rx	After Rx
N1	13.123	12.769	0.081	0.044	0.109	0.051	96.967	95.222	44.70	47.73	55.30	52.27	0.93	1.17
N2	15.288	16.085*	0.081	0.064	0.082	0.084	113.763	119.631*	45.38	42.02	54.62	57.98	1.18	0.72
N3	16.987	16.571	0.223	0.052†	0.080	0.168*	127.323	129.941	54.64	21.21†	45.36	78.79†	2.12	0.39†
REM	15.043	17.730	0.095	0.073	0.079	0.057	111.437	108.907	54.08	54.85	45.92	45.15	1.66	1.64

* $P < 0.05$ in t test; † $P < 0.001$ in t test.

VLf indicates very LF.

TABLE 4. Cognitive Ability Examination Before and After Gabapentin Treatment

Treatment	Logic Memory Test From WMS-III						Stroop Tests on Color Naming						Reaction Time, s																
	Digit Symbol From WAIS-III			Immediate Memory			Delay Memory			Memory Retention			Correction Percentage			Word Color			Word			Color							
	Before	After	Rx	Before	After	Rx	Before	After	Rx	Before	After	Rx	Before	After	Rx	Before	After	Rx	Before	After	Rx	Before	After	Rx					
	Rx	Rx		Rx	Rx		Rx	Rx		Rx	Rx		Rx	Rx		Rx	Rx		Rx	Rx		Rx	Rx						
Mean	9.10	10.95		7.76	10.24		8.00	10.71		74.13	80.16		91.53	93.92		99.60	99.74		97.35	97.88		1.04	1.00		0.53	0.54		0.73	0.69
SD	2.57	3.22		2.74	3.73		3.54	4.22		12.33	15.47		11.54	8.22		1.00	1.21		4.60	3.39		0.35	0.29		0.11	0.11		0.19	0.14
t		-4.605			-5.111			-5.524			-2.168			-1.245			-1.458			-1.249			1.197			-1.338			1.529
P		0.00003			0.00009			0.00002			0.02052			0.14272			0.57638			0.46319			0.16840			0.45875			0.03973

Stroop tests for color naming did not show significant improvement after the treatment in either reaction time or correction percentage of word and color recognition.

DISCUSSION

Gabapentin, originally designed as a precursor of γ -aminobutyric acid that easily enters the brain, has been known to increase brain synaptic γ -aminobutyric acid.²⁹ Recently, the use of gabapentin has been extended into the field of sleep studies on healthy persons, patients with seizure, or alcoholic patients.^{15,30-32} All of these studies, though not on persons with insomnia, are consistent with similar findings of our study showing increased slow-wave sleep. Only 1 article directly examines the effects of gabapentin on chronic insomnia.¹⁶ However, it was a case study report. Our study is a pivotal study of gabapentin's effects on patients with primary insomnia; it was found to improve sleep quality in patients with primary insomnia, as it increases slow-wave sleep and sleep efficiency; it also decreases WASO and spontaneous arousal. These effects are certainly favorable for sleep maintenance. Nevertheless, it may not follow the standard traits of a sleeping pill by inducing rapid onset of initiation of sleep because the latency of sleep onset in our gabapentin trial had no significant change from controls. Therefore, gabapentin may improve the sleep quality with elevated slow-wave sleep and reduced spontaneous arousal, but not well enough for the induction of sleep.

When the EEG power spectrum was analyzed, it revealed the elevation of delta-2 and theta activities in sleep stage N1 after gabapentin treatment. It may be compatible with deepened sleep status even in stage N1. However, its clinical significance is questionable because it is limited to the data in only stage N1. Nevertheless, it was interesting to note the decrease of sigma activities in sleep stages N2 and N3 after gabapentin treatment. The sleep spindle could be a consequence of the prior thalamic inhibition of information processing,³³ and it might be triggered by a sensory stimulus³⁴ during sleep stage 2. Therefore, decreased sigma activity in this study could indicate diminished intrinsic sensory stimulation and lessened efforts of prior thalamic inhibition after gabapentin treatment. These conditions could correspond with decreased spontaneous arousal index in a real-life clinical setting after treatment.

As we analyzed the data of HRV, it revealed significantly decreased spectral power of LF, nuLF%, and nuLF/nuHF ratio in stage N3 and significantly elevated spectral power of HF and nuHF% in sleep stage N3 after treatment. Although it might be inappropriate to consider the nuHF to be a simple measurement of vagal modulation,³⁵ the increasing HF spectrum may be considered to be reflecting the elevation of parasympathetic nervous modulation.²¹ The elevation of the parasympathetic tone could be compatible with significant elevation of slow-wave sleep with increasing percentage of sleep stage N3. The interpretation of the elevation of spectral power of VLF in stage N2 after treatment is not clear because the clinical significance of VLF in HRV is unknown. The increase of total power in stage N2 after treatment is primarily contributed by the elevation of VLF spectral power; therefore, its significance is also uncertain.

After the gabapentin treatment, the prolactin level was noted to be significantly reduced; however, the significance of this is uncertain. It may or may not be related to the gabapentin treatment. Prolactin levels are positively correlated to sleep, particularly slow-wave sleep³⁶ or REM sleep.³⁷ Therefore, the level should decrease once awake. The prolactin level was higher before the gabapentin treatment than it was after the

treatment; that could have been due to prior treatment with a benzodiazepine tranquilizer or benzodiazepine-related hypnotics before entering the gabapentin trial.^{38,39} Once the gabapentin trial had started, if the patient did not take any other medicine, the prolactin level should be reduced. Nevertheless, the direct effect of gabapentin cannot be completely disregarded because the patients with gabapentin treatment were well rested and were able to wake up fully alert without the sleep inertia present in patients with average insomnia.^{40,41}

Gabapentin was originally designed for the treatment of epilepsy. Most antiepileptic medication shows impaired cognitive performance after long-term use.^{42–44} However, recent studies on cognitive effects of gabapentin reveal minimal impact.^{45,46} Our cognitive ability study revealed that not only gabapentin does not impair the cognitive function, but it also improves cognitive ability after treatment, with significant improvement in digit symbol tests, immediate memory, delayed memory, and memory retention in our study. Certainly, both digit symbol and logic memory can be improved because of practice effects of a retest; however, the degree of improvement was so significant that it surely outweighs the variable effects of a retest. Because we did not have a control group for comparison, no definite conclusion can be drawn. The Stroop test and its color naming did not demonstrate an obvious change after the treatment; however, it did not show any evidence of impairment after treatment either. Previous studies have shown improved cognitive function after the improvement of sleep quality and quantity.^{47,48} Therefore, the improvement in cognitive ability after follow-up in gabapentin treatment may be associated with sleep improvements.

In conclusion, this small-scale open-label clinical trial of gabapentin demonstrated the potential of gabapentin to become a supplement treatment of primary insomnia. Its treatment can increase slow-wave sleep along with elevated parasympathetic tone. It can also improve sleep efficiency with decreased spontaneous arousal in sleep maintenance. However, it had no significant influence in sleep initiation or the change of REM sleep. One of the limitations of our study is its small patient group of only 18, which may limit the generalization of the results; in addition, the study did not use a double-blind procedure. Further investigation with a randomized larger-scale double-blind trial would be warranted.

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REFERENCES

- Liappas IA, Malitas PN, Dimopoulos NP, et al. Zolpidem dependence case series: possible neurobiological mechanisms and clinical management. *J Psychopharmacol* 2003;17:131–135.
- Elliot EE, White JM. The acute effects of zolpidem compared to diazepam and lorazepam using radiotelemetry. *Neuropharmacology* 2001;40:717–721.
- Toner LC, Tsambiras BM, Catalano G, et al. Central nervous system side effects associated with zolpidem treatment. *Clin Neuropharmacol* 2000;23(1):54–58.
- Mintzer MZ, Griffiths RR. Selective effects of zolpidem on human memory functions. *J Psychopharmacol* 1999;13:18–31.
- Gordh TE, Stubhaug A, Jensen TS, et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. *Pain* 2008;138:255–266.
- Tanabe M, Takasu K, Takeuchi Y, et al. Pain relief by gabapentin and pregabalin via supraspinal mechanisms after peripheral nerve injury. *J Neurosci Res* 2008;86:3258–3264.
- Gray P. Acute neuropathic pain: diagnosis and treatment. *Curr Opin Anaesthesiol* 2008;21:590–595.
- Tzellos TG, Papazisis G, Amaniti E, et al. Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol* 2008;64:851–858.
- Satija P, Ondo WG. Restless legs syndrome: pathophysiology, diagnosis and treatment. *CNS Drugs* 2008;22:497–518.
- Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin). *Sleep* 1996;19:224–226.
- Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* 2002;59:1573–1579.
- Happe S, Klosch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. *Neurology* 2001;57:1717–1719.
- Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3100 patients in England. *Epilepsia* 2002;43:983–992.
- Rao ML, Clarenbach P, Vahlensieck M, et al. Gabapentin augments whole blood serotonin in healthy young men. *J Neural Transm* 1988;73:129–134.
- Foldvary-Schaefer N, De Leon Sanchez I, Karafa M, et al. Gabapentin increases slow-wave sleep in normal adults. *Epilepsia* 2002;43:1493–1497.
- Rosenberg KP. Gabapentin for chronic insomnia. *Am J Addict* 2003;12:273–274.
- Vollmer KO, Anhut H, Thomann O, et al. Pharmacokinetic model and absolute bioavailability of the new anticonvulsant gabapentin. *Adv Epileptol* 1989;17:209–211.
- Iber C, Ancoli-Israel S, Chesson AL Jr, et al. *The AASM Manual for the Scoring of Sleep and Associated Events*. Westchester, IL: American Academy of Sleep Medicine; 2007.
- Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med* 2006;7:175–218.
- Werth E, Achermann P, Borbely AA. Fronto-occipital EEG gradients in human sleep. *J Sleep Res* 1997;6:102–112.
- Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043–1065.
- Buyse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III digit symbol-coding subtest across the adult lifespan. *Arch Clin Neuropsychol* 2004;19:759–767.
- Kreiner DS, Ryan JJ. Memory and motor skill components of the WAIS-III digit symbol-coding subtest. *Clin Neuropsychol* 2001;15:109–113.
- Tulsky DS, Saklofske DH, Chelune GJ, et al. *Clinical Interpretation of the WAIS-III and WMS-III*. San Diego, CA: Academic Press; 2003.

26. Lichtenberger EO, Kaufman AS, Lai ZC. *Essentials of WMS-III Assessment (Essentials of Psychological Assessment)*. Hoboken, NJ: Wiley; 2001.
27. Uttl B, Graf P. Color-word Stroop test performance across the adult life span. *J Clin Exp Neuropsychol* 1997;19:405–420.
28. Lu PH, Boone KB, Jimenez N, et al. Failure to inhibit the reading response on the Stroop test: a pathognomonic indicator of suspect effort. *J Clin Exp Neuropsychol* 2004;26:180–189.
29. Czapinski P, Blaszczyk B, Czuczwar SJ. Mechanisms of action of antiepileptic drugs. *Curr Top Med Chem* 2005;5:3–14.
30. Ehrenberg B. Importance of sleep restoration in co-morbid disease: effect of anticonvulsants. *Neurology* 2000;54(5 suppl 1):S33–S37.
31. Karam-Hage M, Brower KJ. Gabapentin treatment for insomnia associated with alcohol dependence [comment]. *Am J Psychiatry* 2000;157:151.
32. Bazil CW, Battista J, Basner RC. Gabapentin improves sleep in the presence of alcohol. *J Clin Sleep Med* 2005;1:284–287.
33. Cote KA, Epps TM, Campbell KB. The role of the spindle in human information processing of high-intensity stimuli during sleep. *J Sleep Res* 2000;9:19–26.
34. Sato Y, Fukuoka Y, Minamitani H, et al. Sensory stimulation triggers spindles during sleep stage 2. *Sleep* 2007;30:511–518.
35. Burr RL. Interpretation of normalized spectral heart rate variability indices in sleep research: a critical review. *Sleep* 2007;30:913–919.
36. Spiegel K, Luthringer R, Follenius M, et al. Temporal relationship between prolactin secretion and slow-wave electroencephalic activity during sleep. *Sleep* 1995;18:543–548.
37. Roky R, Obal F Jr, Valatx JL, et al. Prolactin and rapid eye movement sleep regulation. *Sleep* 1995;18:536–542.
38. Copinschi G, Van Onderbergen A, L'Hermite-Baleriaux M, et al. Effects of the short-acting benzodiazepine triazolam, taken at bedtime, on circadian and sleep-related hormonal profiles in normal men. *Sleep* 1990;13:232–244.
39. Copinschi G, Akseki E, Moreno-Reyes R, et al. Effects of bedtime administration of zolpidem on circadian and sleep-related hormonal profiles in normal women. *Sleep* 1995;18:417–424.
40. Ferrara M, De Gennaro L. The sleep inertia phenomenon during the sleep-wake transition: theoretical and operational issues. *Aviat Space Environ Med* 2000;71:843–848.
41. Ferrara M, Curcio G, Fratello F, et al. The electroencephalographic substratum of the awakening. *Behav Brain Res* 2006;167:237–244.
42. Meador K, Loring D, Gallagher B et al. Comparative cognitive effects of anticonvulsants. *Neurology* 1990;40:391–394.
43. Aldenkamp A. Effects of antiepileptic drugs on cognition. *Epilepsia* 2001;42(suppl 1):46–49.
44. Meador K, Gilliam F, Kanner A, et al. Cognitive and behavioral effects of antiepileptic drugs. *Epilepsy Behav* 2001;4:SS1–SS17.
45. Salinsky MC, Storzbach D, Spencer DC, et al. Effects of topiramate and gabapentin on cognitive abilities in healthy volunteers. *Neurology* 2005;64:792–798.
46. Marin R, Kuzniecky R, Ho S, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 1999;52:321–327.
47. Hunter P. To sleep, perchance to live. Sleeping is vital for health, cognitive function, memory and long life. *EMBO Rep* 2008;9:1070–1073.
48. Fulda S, Shulz H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev* 2001;5:423–445.