

## Gabapentin Increases Slow-wave Sleep in Normal Adults

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**Summary:** *Purpose:* The older antiepileptic drugs (AEDs) have a variety of effects on sleep, including marked reduction in rapid-eye-movement (REM) sleep, slow-wave sleep (SWS), and sleep latency, and an increase in light sleep. The effects of the newer AEDs on sleep are unknown. Our purpose was to study the effect of gabapentin (GBP) on sleep.

*Methods:* Ten healthy adults and nine controls were the subjects of this study. All underwent baseline and follow-up polysomnography (PSG) and completed sleep questionnaires. After baseline, the treated group received GBP titrated to 1,800 mg daily. Polygraphic variables and Epworth Sleepiness Scale (ESS) scores, a subjective measure of sleep propensity, were compared by using the Wilcoxon signed rank test.

*Results:* Nine of the treated subjects achieved the target dose; one was studied with 1,500 mg daily because of dizziness experienced at the higher dose. GBP-treated subjects had an increase in SWS compared with baseline. No difference in the ESS or other polygraphic variables was observed. However, a minor reduction in arousals, awakenings, and stage shifts was observed in treated subjects.

*Conclusions:* GBP appears to be less disruptive to sleep than are some of the older AEDs. These findings may underlie the drug's therapeutic effect in the treatment of disorders associated with sleep disruption. **Key Words:** Gabapentin—Sleep architecture—Polysomnography—Antiepileptic drugs—Daytime sleepiness.

Individuals with epilepsy commonly report excessive daytime sleepiness (EDS) and fatigue that are typically attributed to the effects of seizures or antiepileptic drugs (AEDs). However, in patients with epilepsy, sleep is disrupted by frequent arousals, awakenings, and stage shifts, even in the absence of seizures and AEDs (1). Daytime and nocturnal seizures fragment sleep, reducing the percentage of rapid-eye-movement (REM) sleep and slow-wave sleep (SWS) (1,2). Many of the older AEDs reduce the percentage of REM and SWS and increase arousals, awakenings, and stage shifts, suggesting a tendency for sleep fragmentation. The effects of the newer AEDs on sleep have not been adequately studied.

Approved by the Food and Drug Administration (FDA) in 1993 for the treatment of partial seizures, gabapentin (GBP) is currently used in the treatment of a variety of disorders associated with sleep disruption including psychiatric disorders, restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), headache, neuropathic pain syndromes, and movement disorders (3). Whether the drug's effects are due to changes in sleep quality or quantity is unknown. The

purpose of this study was to investigate the effects of GBP on sleep architecture and daytime vigilance in normal adults.

### METHODS

#### Subjects

This study was approved by the Institutional Review Board of the Cleveland Clinic Foundation. Ten healthy adults between the ages of 18 and 45 years participated. Exclusion criteria included (a) use of barbiturates, benzodiazepines (BZDs), ethanol, antihistamines, recreational drugs, and prescription and nonprescription sleep aids within 30 days of enrollment and for the duration of the study; (b) evidence of a sleep disorder based on clinical history or polysomnography (PSG), other than primary snoring; and (c) psychiatric disorder or Beck Depression Inventory (BDI) score of  $\geq 15$  or higher (4). Female subjects of childbearing potential were required to practice an acceptable method of birth control, as indicated in the informed consent document. Nine subjects who underwent ambulatory PSG for purposes of studying first-night effect in the home served as a control group.

#### Baseline phase

After giving written informed consent, subjects were interviewed by a board-certified sleep medicine physi-

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cian and instructed on the maintenance of sleep logs. Subjects completed a 17-item questionnaire designed to ascertain sleep patterns and sleep disorder symptoms, the Epworth Sleepiness Scale (ESS), and the BDI. The sleep questionnaire included the average number of hours of sleep per night, sleep latency, number of awakenings and their cause, napping habits, caffeine use, and sleep disorder symptoms such as snoring, witnessed apnea, difficulty initiating or maintaining sleep, restlessness, and uncomfortable sensations in the legs in the evening relieved by movement. The ESS is an eight-item survey designed to ascertain sleep propensity during activities of daily living (5). Subjects rate the chance of dozing in each of eight activities of daily living from 0 (never) to 3 (high). The scores for the eight activities are tallied, producing a total score ranging from 0 to 24, with 24 indicating severe daytime sleepiness. The BDI was administered to screen for depression, a common cause of sleep disruption.

Subjects underwent a baseline home PSG by using the Digitrace SleepScan. This system incorporates four EEG channels (C3, C4, O1, O2), two electrooculogram (EOG) channels (right and left outer canthus), chin and anterior tibialis electromyogram (EMG), electrocardiogram (ECG), airflow, respiratory effort (thoracic and abdominal), oxygen saturation, body position, and snoring. After the PSG, subjects rated their sleep as the same, worse, or better as compared with usual.

### Titration phase

After collecting baseline data, we administered GBP according to the schedule shown below. All subjects began at a daily dose of 300 mg and were titrated to 1,800 mg per day (600 mg, thrice daily).

Day 1: 300 mg q a.m.

Day 2: 600 mg (300 mg b.i.d.)

Day 3: 900 mg (300 mg t.i.d.)

Day 4: 1,200 mg (600 mg a.m.; 300 mg midday; 300 mg at bedtime)

Day 5: 1,500 mg (600 mg a.m.; 600 mg midday; 300 mg at bedtime)

Days 6–16: 1,800 mg (600 mg t.i.d.)

### Posttreatment phase

GBP-treated subjects underwent a second PSG 7–10 days after achieving the target or highest tolerated dose. A blood sample was obtained for GBP concentration on the following morning. The ESS and a posttreatment questionnaire, designed to ascertain subjective changes in sleep quality or daytime alertness during the treatment period, were completed by all subjects at the time of the second PSG. Sleep logs were maintained for the duration of the study. Control subjects underwent two ambulatory PSGs 2 weeks apart and completed questionnaires and sleep logs as described above.

### Data analysis

PSGs were scored by a board-certified R.PSGT. and interpreted by the first author by using standard scoring procedures (6). PSG variables included total sleep time (TST; time occupied by stages 1, 2, 3, 4, and REM, in minutes), sleep latency (SL; time from lights out to sleep onset, defined as the first of three consecutive epochs of stage 1 sleep or one epoch of any other stage, in minutes), sleep efficiency (SE; TST divided by time in bed, expressed as a percentage), REM latency (time from sleep onset to the first epoch of REM sleep, in minutes), percentage TST spent in nonREM stages 1, 2, and slow-wave sleep (SWS, stages 3 and 4 combined), and REM sleep, number of stage shifts, awakenings (return of waking background rhythm for  $\geq 30$  s) and REM periods, arousal index (number of arousals per sleep hour), apnea–hypopnea index (AHI; number of apneas and hypopneas per sleep hour), periodic limb movement index (PLMI; number of periodic limb movements per sleep hour), and periodic limb movement arousal index (PLMAI; number of periodic limb movements causing arousal per sleep hour). Mean sleep time per night was determined at baseline and follow-up by averaging the number of sleep hours per night recorded in logs during the week preceding each PSG. The randomized groups were compared on change from baseline by using the Wilcoxon rank-sum test. This test was used to determine whether the change was nonzero within the group. A *p* value of  $<0.05$  was considered to be statistically significant. The SAS statistical software was used to perform all analyses.

## RESULTS

The mean age was 32 years (20–46 years) for GBP-treated and 35 years (30–45 years) for control subjects. One of the treated subjects was unable to tolerate 1,800 mg daily because of dizziness but completed the study, taking 1,500 mg per day. Mean baseline and follow-up ESS scores were 5.9 versus 6.1 for GBP-treated subjects and 5.22 versus 4.75 for controls (NS). Mean sleep time per night based on sleep logs at baseline and follow-up was 7.36 versus 7.66 for GBP-treated and 7.24 versus 6.99 for control subjects (NS). Mean GBP concentration was 5.47  $\mu\text{g/ml}$ .

Polygraphic variables are shown in Table 1. A significant increase in SWS was observed in GBP-treated subjects compared with baseline. However, the change from baseline to follow-up in SWS percentage between the groups was not statistically significant. All of the GBP-treated subjects and six (67%) of the control subjects had an increase in SWS percentage. A decrease in arousals, awakenings, and stage shifts not reaching statistical significance were observed in the GBP-treated group, suggesting a tendency toward sleep consolidation. No

TABLE 1. Polysomnographic variables

Sleep variable	Gabapentin (n = 10)			Controls (n = 9)		
	Baseline	Follow-up	p <sup>a</sup>	Baseline	Follow-up	p <sup>a</sup>
Total recording time (min)	417.3 ± 57.44	420.7 ± 71.76	0.90	404.4 ± 63.44	430.69 ± 47.41	0.33
Total sleep time (min)	386.3 ± 56.51	397.7 ± 72.33	0.69	380.38 ± 55.32	401.51 ± 47.14	0.41
Sleep efficiency (%)	92.0 ± 0.03	93.0 ± 0.03	0.50	93.0 ± 0.04	90.0 ± 0.06	0.19
Sleep latency (min)	16.7 ± 8.98	15.9 ± 7.75	0.81	14.78 ± 9.23	16.70 ± 8.98	0.13
REM latency (min)	79.1 ± 24.74	80.0 ± 26.26	0.92	80.22 ± 28.36	84.78 ± 30.63	0.73
Stage 1 (%)	8.0 ± 0.03	8.0 ± 0.05	0.81	8.0 ± 0.05	10.0 ± 0.04	0.32
Stage 2 (%)	62.0 ± 0.06	57.0 ± 0.05	0.07	61.0 ± 0.07	59.0 ± 0.03	0.59
Stage 3–4 (%)	8.0 ± 0.05	13.0 ± 0.07	0.007 <sup>b</sup>	8.0 ± 0.05	9.0 ± 0.06	0.60
REM (%)	22.0 ± 0.04	22.0 ± 0.07	0.80	23.0 ± 0.06	22.0 ± 0.04	0.59
REM periods	4.0 ± 0.94	3.9 ± 0.99	0.78	3.56 ± 0.88	4.0 ± 1.22	0.31
Stage shifts	75.2 ± 20.91	62.7 ± 29.77	0.20	69.11 ± 12.82	78.78 ± 20.78	0.21
Awakenings (number/night)	7.20 ± 3.52	4.70 ± 5.76	0.12	5.11 ± 2.80	6.22 ± 3.38	0.39
Arousal index	6.4 ± 2.90	5.8 ± 2.21	0.48	9.0 ± 5.87	5.66 ± 2.59	0.85
Apnea–hypopnea index	0.32 ± 0.73	0.59 ± 0.81	0.36	0.32 ± 0.60	0.13 ± 0.27	0.24
PLM index	2.82 ± 6.21	0.53 ± 1.62	0.15	5.69 ± 10.87	2.03 ± 5.80	0.12
PLMA index	0.15 ± 0.25	0.00	0.10	0.24 ± 0.62	2.0 ± 0.05	0.28

REM, rapid-eye-movement sleep; PLM, periodic limb movements; PLMA, PLM arousal.

<sup>a</sup> Comparing follow-up to baseline within groups.

<sup>b</sup> Significant after Bonferroni correction.

significant difference in sleep variables from baseline to follow-up between GBP and control groups or between baseline and follow-up PSGs of the control group was observed.

Six treated subjects reported no change in sleep quality or daytime alertness with GBP, whereas two described a reduction in sleep latency and/or nocturnal awakenings compared with baseline. More frequent naps and an increase in dreaming were reported by one subject each.

## DISCUSSION

Our study demonstrates a significant increase from baseline in SWS in normal adults treated with GBP at doses generally considered to be effective in the treatment of epilepsy. However, this increase was not statistically different from that of control subjects. Stable REM percentage and a mild reduction in arousals, awakenings, REM periods, and stage shifts, features of sleep fragmentation, also are noteworthy findings. Increased SWS percentage was reported in healthy subjects taking GBP at doses as low as 600 mg daily (7) and patients with PLMD (8). Increased TST and SE and a reduction in arousals and awakenings also were observed in the latter group (8). Subjective improvements in sleep quality and daytime alertness have been reported by GBP-treated patients with epilepsy, RLS, PLMD, and migraine (8,9).

Placidi et al. (10) recently compared sleep architecture in 10 patients with poorly controlled epilepsy at baseline and after 3 months of GBP 1,800 mg/day. All but one were receiving polytherapy, including drugs with REM-suppressing properties. Nevertheless, GBP treatment was associated with a significant increase in REM sleep and

REM periods and a decrease in awakenings and stage 1 sleep in the setting of a mild reduction in seizures and no change in interictal spike rate, suggesting that their findings were not due exclusively to an improvement in epilepsy. Variations in the composition of study groups likely explain the differences between these results and our findings. Although normal in our cohort, baseline REM percentage was markedly reduced in the study of Placidi et al. (10), likely due to the effects of seizures and concomitant AEDs. Second, even though subjects were studied during a 24-h seizure-free period, the patients in the prior study had medically intractable epilepsy, which likely produced an effect on sleep continuity from night to night.

GBP is an amino acid, originally synthesized as a structural analogue of  $\gamma$ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Although structurally similar to GABA, the drug does not bind to GABA receptors or inhibit the uptake or degradation of GABA and is not metabolized into GABA or GABA agonists (11). However, GBP increases the rate of GABA synthesis in several regions of the rat brain, suggesting that the drug does alter GABA metabolism (12). Brain GABA levels measured by <sup>1</sup>H magnetic resonance spectroscopy (MRS) were elevated in the occipital cortex in GBP-treated patients with epilepsy (13). Levels of GABA are increased in the septal nucleus and basal forebrain of cats during REM sleep (14), and electrical stimulation of this area induces sleep in animals.

GBP also may affect sleep and vigilance through serotonergic mechanisms. For many years, serotonin has been known to play a role in the modulation of sleep. Early studies suggested that the neurotransmitter was necessary to achieve and maintain sleep (15). However,

more recent animal experiments found higher serotonin levels during waking than in nonREM and REM sleep (15,16). That stimulation of serotonin receptors in cholinergic neurons of the basal forebrain increases rhythmic burst activity mediated by low-threshold calcium spikes (17) and microinjection of serotonin into the nucleus basalis in rats increases slow wave activity (18) support a relation between serotonin and the generation of SWS. In the only human study, SWS and blood serotonin levels increased in six healthy male subjects treated with 600 to 900 mg daily of GBP for 3 days (7). These findings are particularly intriguing in view of our results, and together support a serotonergic mechanism in the effects of GBP on the sleep/wake cycle.

A variety of PSG variables may be used to ascertain sleep fragmentation. Sleep disruption is common on the first night in a series of overnight PSGs performed in the sleep laboratory, a phenomenon known as the "first-night effect" (19,20). These changes include reduced efficiency of sleep, increased light sleep (stage 1), prolonged latency to sleep, prolonged REM latency, increased REM periods, stage shifts, arousals and awakenings, and reduced SWS and REM sleep. Because the first-night effect is virtually absent when PSG is performed in the home (19,20), we used ambulatory PSG instead of attended laboratory studies, the current gold standard used for the diagnosis of sleep disorders. The number of channels and recording parameters were similar to those in laboratory studies. Although a major limitation of home recordings is the risk of data loss due to artifact or electrode/sensor dysfunction, in the experience of our laboratory and others, data loss due to equipment failure has not occurred (21).

The interpretation of prior studies addressing the effects of AEDs on sleep is limited because of methodologic variations, including composition of the study population, dose, timing and duration of treatment, and failure to control for seizures and concomitant AEDs. For these reasons, and because GBP is being used with increasing frequency for the treatment of disorders other than epilepsy, we chose to study the effects of the drug on sleep in a normal, healthy population. The older AEDs have been shown to have a variety of effects on sleep. Phenobarbital (PB) reduces sleep latency and REM sleep and increases sleep efficiency and light (stage 1 and 2) nonREM sleep (22). The effects of phenytoin (PHT) and carbamazepine (CBZ) appear to vary with treatment duration. Short-term PHT therapy (time to steady state) produces a reduction of sleep latency and stage 1 and increases in SWS and arousals, which reverses after several months of treatment (23). Similarly, a single dose of controlled-release CBZ produced a reduction in REM and increase in REM fragmentation that was no longer observed after 1 month of treatment (24). Prolonged CBZ treatment has been shown to reduce

REM sleep in patients with temporal lobe epilepsy (9). The effects of valproate (VPA) on sleep range from a reduction in REM and increase in SWS to none (25,26). In contrast, lamotrigine (LTG), another newer AED effective in the treatment of epilepsy and psychiatric disorders, appears to have more consolidating effects on sleep, stabilizing REM sleep and reducing arousals and stage shifts (9,27).

Our findings suggest that GBP may be less disruptive to sleep than many of the older AEDs, which have previously been shown to produce a shift toward light sleep, reduced sleep efficiency, prolonged sleep latency, and an increase in arousals and awakenings. These alterations in sleep architecture may contribute to the drug's effects in disorders associated with sleep disruption.

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