

SCIENTIFIC INVESTIGATIONS

## Gabapentin Improves Sleep in the Presence of Alcohol

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**Study Objectives:** To evaluate the ability of a single dose of gabapentin to improve sleep disruption caused by alcohol consumption.

**Methods:** Double-blind, randomized, single-dose, crossover study of normal subjects (age 21-45 years) who were free of known sleep disorders or medical conditions that could interfere with sleep. Subjects first received baseline polysomnography and, upon awakening, subjective scales of drowsiness and functioning. One to 2 weeks later, they returned to the sleep lab. They consumed 4 ounces of 40% alcohol and gabapentin (300 or 600 mg) or placebo 1 hour prior to bedtime. Polysomnography and subjective scales were repeated. One to 2 weeks later, subjects returned and were given the same dose of alcohol and the other treatment, followed by repeat testing. Differences between baseline and placebo (alcohol) results were compared to the difference between baseline and gabapentin (alcohol) by paired *t* tests.

**Results:** Thirteen subjects were enrolled; 12 completed the study. Mean age was 30.8 years (range 25-37 years). No difference in total sleep time was

seen for any of the groups. Gabapentin (300 or 600 mg) showed a significant decrease in stage 1 (9.3% vs 5.5%) and number of awakenings (11 vs 6) with increased sleep efficiency (93% vs 96.2%). Subjects receiving 600 mg also showed increased slow wave sleep, decreased rapid eye movement sleep, and decreased arousals. No differences were seen in any of the subjective tests of drowsiness and performance.

**Conclusions:** Single-dose gabapentin at bedtime can improve sleep through decreased stage 1 sleep, increased slow-wave sleep, increased sleep efficiency, and decreased arousals. Gabapentin may be useful in the treatment of conditions in which frequent awakenings and decreased sleep efficiency are seen.

**Keywords:** Gabapentin, alcohol, slow wave sleep, sleep efficiency, sleep disruption

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Sleepiness is common in the United States, and over 20% of Americans report sleepiness sufficient to interfere with daily activities at least several days per week.<sup>1</sup> This is not a benign condition but is associated with decreased concentration and increases in cardiovascular disease and accidents and an overall increase in mortality.<sup>2,3</sup> Sleepiness has many causes, including a number of conditions resulting in impaired sleep onset, difficulty with sleep maintenance, or nonrestorative sleep. These causes of sleepiness are most commonly treated pharmacologically,<sup>4,5</sup> with hypnotic, anxiolytic, and antidepressant medications prescribed most often.<sup>5,6</sup> Although these agents may decrease sleep latency and the number of arousals, they do not increase the overall quality of sleep. In fact, benzodiazepines decrease rapid eye movement (REM) and slow-wave sleep (SWS), and most antidepressant medications (tricyclic antidepressants and selective serotonin reuptake inhibitors) also decrease REM sleep.<sup>7</sup> This is potentially important because REM sleep and SWS are required for certain forms of learning.<sup>8</sup> Furthermore, treatment with benzodiazepines generally results in tolerance to hypnotic effects. In many condi-

tions, therefore, it might be useful to use agents that improve sleep continuity or structure without producing somnolence; however none are presently available.

Gabapentin is a compound widely used in the treatment of epilepsy<sup>9</sup> and neuropathic pain.<sup>10,11</sup> A number of studies, in both patients and normal subjects, have shown an increase in SWS, decreased number of awakenings, and increased sleep efficiency with this drug.<sup>12-14</sup> Gabapentin may therefore be an entirely novel treatment for a variety of conditions that cause problems with sleep maintenance, including psychophysiologic insomnia and obstructive sleep apnea. Because alcohol consumed at bedtime is known to cause an increase in the number of awakenings and a decreased amount of SWS,<sup>15,16</sup> administration of alcohol to normal subjects forms a convenient model for sleep disruption that could potentially be reversed by a drug with the properties of gabapentin. If effective, studies in other forms of sleep disruption would be appropriate. This study looks at the ability of gabapentin to improve or reverse sleep disruption caused by alcohol consumption.

### METHODS

This was a double-blind, randomized, single-dose, crossover study of normal subjects. Subjects were recruited by fliers and word of mouth within the medical center. They were between the ages of 21 and 45 years and had no known sleep disorder and no history of alcoholism. Each was screened for any medical conditions or sleep disorders that could interfere with results. Women of childbearing potential could not be pregnant, and urine pregnancy tests were administered to all women of childbearing potential before each administration of the study medication or alcohol. Any

### Disclosure Statement

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serious medical condition that the investigator deemed a risk for administration of either alcohol or gabapentin also excluded subjects from the trial. This included, but was not limited to, peptic ulcer disease, gastritis, alcoholism, and hepatic disease. Gabapentin and matching placebo were provided and randomized by the research pharmacy of Columbia University. All subjects received both placebo and gabapentin, in random order; each subject was randomly assigned to receive either a 300-mg or a 600-mg dose of gabapentin. Sleep logs were maintained by all subjects for 1 week before each overnight polysomnogram; however, activity monitors were not used.

Testing occurred on 3 nights. Patients first received baseline polysomnography. Subjects arrived at the laboratory between 7 and 9 PM in preparation for the studies. Lights out was between 10 and 12 PM, and studies ended with spontaneous awakening between 6 and 8 AM. As much as possible, this was scheduled to coincide with each subject's habitual bedtime. Polysomnography was scored by a single investigator blinded to drug-treatment arm (gabapentin or placebo) and to gabapentin dose. Standard recording was used and included four electroencephalogram channels, electrooculogram, electromyogram (chin and legs), nasal airflow, chest and abdomen movements, electrocardiogram, and oxygen saturation. Sleep was staged according to standard technique.<sup>17</sup> Awakenings were defined as at least 1 epoch scored as awake after a sleep period; arousals were defined as a shift to higher electroencephalogram frequencies during a sleep epoch without progression to full wakefulness, according to the criteria of the American Sleep Disorders Association.<sup>18</sup> Between 2 and 4 hours after awakening, subjects filled out the Stanford Sleepiness Scale and 6 linear analogue scales measuring alertness, ability to function, effectiveness at work, mood, concentration, and creative thinking. These tests have been used in other studies and are sensitive to the effects of hypnotic medications.<sup>19,20</sup> These were not given immediately after awakening so that maximal wakefulness would be measured.

One to 2 weeks later, subjects returned to the sleep lab. They consumed 4 ounces of 40% alcohol (vodka) in orange juice 1 hour prior to bedtime and were given a single-dose drug (gabapentin, 300 or 600 mg) or placebo in a randomized, double-blind fashion immediately afterward. Alcohol was consumed over a maximum 15-minute period. Subjects did not eat between arrival and alcohol consumption; therefore, there was a minimum of 2 hours between last meal and alcohol consumption. Polysomnography and subjective scales were repeated. One to 2 weeks later, subjects returned and were given the same dose of alcohol and drug or placebo, again followed by repeat testing. For each sleep param-

eter, the difference between baseline and placebo (with alcohol) results were compared to the difference between baseline and gabapentin (with alcohol) by paired t tests. Analysis was performed for subjects receiving 300 mg of gabapentin, for subjects receiving 600 mg of gabapentin, and for all subjects pooled together.

## RESULTS

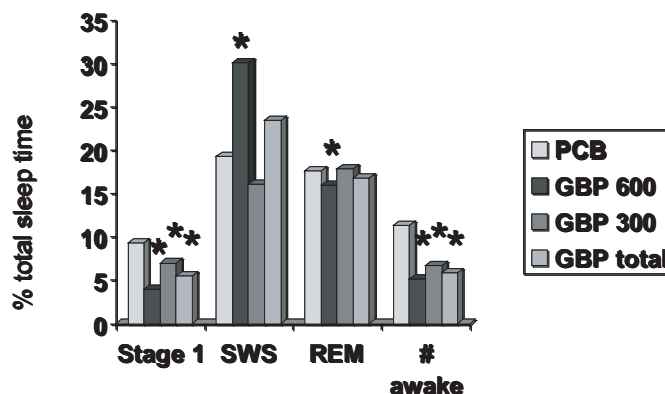
A total of 13 subjects were enrolled in the study; 1 withdrew after the baseline study (due to a scheduling conflict); therefore, 12 subjects completed the study. There were no reported adverse events. Nine subjects were women. Mean age was 30.8 years (range 25-37 years).

No difference in total sleep time was seen for any of the groups (baseline vs alcohol or alcohol-placebo vs alcohol-gabapentin). Effects of alcohol on sleep are shown in the Table 1. There was no significant change in any of the studied parameters. The effects of gabapentin on sleep are shown in the Figure 1. When all gabapentin doses were considered together, there was a significant reduction in the percentage of stage 1 sleep and number of awakenings, an increase in sleep efficiency (93.0%  $\pm$  1.1% vs 96.2%  $\pm$  0.9% for placebo vs gabapentin, respectively), and no change in other parameters. For the subgroup receiving 600 mg of gabapentin, the decrease in the percentage stage 1 sleep and the number of awakenings persisted, and arousals also decreased (29  $\pm$  7 vs 17  $\pm$  5). There was a significant increase in percentage of SWS and a decrease in REM sleep. Sleep efficiency increased, although this did not reach statistical significance. For the subgroup receiving only 300 mg of gabapentin, a reduction in stage 1 sleep and in the number of awakenings was seen; other changes did not reach statistical significance.

No differences were seen in the Stanford Sleepiness Scales (3  $\pm$  0.7 vs 3  $\pm$  0.3 for placebo vs drug) or in any of the subjective tests of drowsiness and performance given the mornings after polysomnography (data not shown), and no trends were evident.

## DISCUSSION

This study shows improvement in a number of aspects of sleep



**Figure 1**—Effect of gabapentin on various sleep parameters. Results for placebo are the sum of subjects receiving 300 or 600 mg gabapentin. \* $p < .05$  for baseline minus treatment versus baseline minus placebo. SWS refers to percentage of slow wave sleep; REM, percentage of rapid eye movement sleep; # awake: number of awakenings; PCB, placebo; GBP, gabapentin.

**Table 1**—Effects of Alcohol on Sleep

Parameter	Condition		
Sleep stage, %	Baseline	Alcohol	
	1	8.1 $\pm$ 1.4	9.3 $\pm$ 1.1
	SWS	19.4 $\pm$ 2.0	19.3 $\pm$ 1.7
	REM	19.0 $\pm$ 1.3	17.6 $\pm$ 1.4
Sleep efficiency, %	92.3 $\pm$ 1.9	93.0 $\pm$ 1.1	
Total sleep time, min.	368.96 $\pm$ 7.4	382.42 $\pm$ 12.2	
Awakenings, no.	9.7 $\pm$ 1.7	11.3 $\pm$ 1.5	
Arousals, no.	33.6 $\pm$ 8.8	30.8 $\pm$ 5.3	

Data are presented as mean  $\pm$  SD. SWS refers to slow-wave sleep; REM, rapid eye movement.

in alcohol-treated subjects when a single dose of gabapentin is given at bedtime. In studies using similar amounts of alcohol without gabapentin treatment, stage 3 SWS was decreased by almost 25%,<sup>15</sup> sleep efficiency was decreased from 86% to 81%, and wake time after sleep onset increased from 39 to 67 minutes.<sup>16</sup> Sample sizes were similar to our study (6 and 10 subjects); however, both of these studies used at least 1 adaptation night in the sleep laboratory prior to baseline or alcohol condition. In our study, alcohol did not produce significant sleep disruption. This may be an artifact of our design; the baseline night was performed in the naïve patients without an adaptation study, with the alcohol comparison in a subsequent study. Subjects may therefore have had a “first-night effect,”<sup>21</sup> resulting in sleep disruption in the absence of alcohol, with a consequent masking of an alcohol effect. The sample size may also have been too small to detect sleep disruption with the amount of alcohol used.

This study does show clear differences in the sleep of alcohol-treated subjects in the presence of gabapentin. All gabapentin subjects showed decreased sleep disruption, manifest by improvement in sleep efficiency, number of awakenings, and stage 1 sleep. The subgroup who received a higher dose of gabapentin also showed an increase in SWS and a decrease in stage 1 sleep. REM sleep was decreased, and this was statistically significant with the 600-mg dose. No differences in subjective measures of wakefulness were seen; it may be that evaluation closer to waking (rather than 2-4 hours used in this study) would show a difference.

These findings are consistent with those of earlier studies in epilepsy patients and in normal subjects undergoing chronic treatment with gabapentin. These showed a decreased number of awakenings and percentage of stage 1 sleep<sup>12</sup> and increased percentage of SWS.<sup>13,14</sup> One of these studies also showed increased REM sleep.<sup>12</sup> All of these studies dosed gabapentin chronically, 3 times daily. Our study shows that similar improvements in sleep can be obtained with a single dose of gabapentin administered at bedtime in normal subjects and that these effects are present immediately. Unfortunately, performance tests were not used in this study; further investigations should use these to clarify the clinical relevance of any observed changes in sleep.

With this in mind, gabapentin could be useful in the treatment of conditions in which frequent awakenings and decreased sleep efficiency are seen, including psychophysiologic insomnia and obstructive sleep apnea. Effectiveness has already been shown for sleep disruption in chronic pain<sup>10,11</sup> and periodic limb movements of sleep.<sup>22</sup> A structurally and functionally related compound, pregabalin, also improves sleep in patients with postherpetic neuralgia<sup>23</sup> and diabetic neuropathy.<sup>24</sup> It may be that 600 mg of gabapentin is more effective, based on our preliminary data. It is unclear, however, whether the improvements seen in this study would be clinically significant. Also, sleep was not highly disrupted in these subjects; it could be that patients with more severe sleep disruption would show more (or less) benefit. Possible effects of gabapentin on other sleep disorders would therefore need to be investigated with randomized trials in each specific disorder, ideally including measures of daytime performance and long-term efficacy and tolerability. Effects of chronic treatment would also need to be studied. However, if effective, gabapentin could provide a much-needed, nonsedative medication option for the many patients with disorders of sleep continuity.

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