A Pilot Study on the Effects of Sodium Oxybate on Sleep Architecture and Daytime Alertness in Narcolepsy

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Study Objectives: To measure the effect of nocturnal sodium oxybate administration on sleep architecture in patients with narcolepsy.

Design: Open-label study.

Setting: Four accredited sleep clinics.

Participants: 25 adult patients with narcolepsy-cataplexy.

Interventions: Patients were weaned from previously used anticataplectic medications and administered increasing nightly doses of sodium oxybate over a 10-week period: 4.5 g for 4 weeks, 6 g for 2 weeks, 7.5 g for 2 weeks, and 9 g for 2 weeks. The effect of sodium oxybate was measured using nocturnal polysomnograms, the Epworth Sleepiness Scale, the Maintenance of Wakefulness Test, and a narcolepsy symptoms questionnaire.

Results: The nightly administration of sodium oxybate produced dose-related increases in slow-wave sleep and delta power, rapid eye movement sleep increased initially and then decreased in a dose-related manner, nocturnal awakenings decreased, and daytime sleep latency increased. Significant improvements in daytime symptoms were measured by the Maintenance of Wakefulness Test, the Epworth Sleepiness Scale, and the narcolepsy symptom questionnaire.

Conclusions: Nocturnal administration of sodium oxybate in patients with narcolepsy produces significant improvements in sleep architecture, which correlate with improvements in daytime narcolepsy symptoms.

INTRODUCTION

PREVIOUS STUDIES HAVE DEMONSTRATED THAT THE NOCTURNAL ADMINISTRATION OF SODIUM OXYBATE SIGNIFICANTLY DECREASES THE OCCURRENCE OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY.1-5 These studies have shown that sodium oxybate reduces the need for antidepressant drugs for the treatment of cataplexy and limits the dose of stimulant medication required during the day. Moreover, in contrast to treatment with conventional anticataplectic agents, tolerance to the beneficial effects of sodium oxybate does not occur with prolonged use.6 Although little is known about the mechanism of action of sodium oxybate in narcolepsy, it consistently produces subjective improvement in nocturnal sleep and daytime alertness. The following pilot study was performed to test the hypothesis that the nocturnal administration of sodium oxybate is associated with dose-related changes in sleep architecture, which correlate with improvements in daytime narcolepsy symptoms.

METHODS

Subjects

Subjects qualified for the study if they were at least 18 years of age and had positive diagnosis of narcolepsy based upon a valid polysomnographic recording and Multiple Sleep Latency Test performed within the previous 5 years. Subjects were eligible if they were taking a stable dose of tricyclic antidepressant or a selective serotonin reuptake inhibitor for the treatment of cataplexy for at least 3 weeks before the beginning of the trial; taking either a stimulant at a stable dose or taking no stimulant for at least 3 weeks before the beginning of the trial; if female, either surgically sterile, 2 years postmenopausal, or using a medically accepted method of birth control; able to provide evidence for adequate social support during the trial; willing to forgo operating a car or heavy machinery during the trial if the investigator deemed this necessary; and willing to provide informed consent to participate in the trial.

Subjects were excluded from the trial if they had used sodium oxybate or any other investigational drug within 30 days of the start of the trial; used tricyclic antidepressants or selective serotonin reuptake inhibitors for symptoms other than those related to narcolepsy; any physical or mental illness that placed the subject at risk or prevented them from completing the trial; had a myocardial infarction within 6 months of the start of the trial; a history of a seizure disorder, head trauma or invasive intracranial surgery; a current history of a substance abuse disorder; symptoms of daytime drowsiness caused by disorders other than narcolepsy, such as obstructive sleep apnea; an occupation requiring variable work hours or night-shift work; abnormal laboratory findings, such as a serum creatinine greater than 2.0 mg/dL,
amino alanine transferase or aspartate amino transferase values greater than twice the upper limit of normal, a serum bilirubin greater than 1.5 times the upper limit of normal; or an abnormal electrocardiogram.

Before beginning the study, all subjects provided a medical history and underwent a physical examination as well as clinical laboratory testing to collect the following data: complete blood cell count, blood urea nitrogen, creatinine, serum glucose, electrolytes, total serum protein, serum albumin, amino alanine transferase, aspartate amino transferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, and a pregnancy test, if applicable.

These test data were obtained again at the completion of the trial.

**Study Design**

The trial took place over a 14-week period (Figure 1). Visit 1 consisted of an overnight polysomnogram (PSG) followed by the maintenance of wakefulness test (MWT) the next day. During the subsequent 2 weeks, subjects were gradually withdrawn from any antidepressant and sedative-hypnotic drugs. This was followed by an additional 2-week washout period. Subjects were allowed to remain on stable doses of their pretrial stimulant medication. At the end of these 4 weeks (Visit 2a), patients underwent a repeat overnight PSG, which represented the baseline for subsequent PSG measures. This was followed by a MWT the next day and another overnight PSG that evening (Visit 2b) when patients were administered sodium oxybate 2.25 g at bedtime and again 4 hours later.

Subjects were provided a supply of sodium oxybate oral solution, which they continued to take on an outpatient basis at the same dose of 2.25 g twice nightly for the next 4 weeks when they returned to the sleep laboratory (Visit 3). At that time, they underwent a nocturnal PSG while taking sodium oxybate 2.25 g twice nightly followed by a MWT the next day. Subsequently, the dose of sodium oxybate was increased to 3.0 g twice nightly for 2 weeks, 3.75 g twice nightly for 2 weeks, and 4.5 g twice nightly during the final 2 weeks of the study. An overnight PSG was performed at the end of each of these 2-week periods (Visits 4, 5, and 6), and a final MWT followed the overnight PSG at Visit 6. Sodium oxybate was administered in the form of a commercially prepared oral solution (Xyrem®, Orphan Medical, Inc., Minnetonka, Minn) consisting of sodium oxybate 500 mg/mL, adjusted to neutral pH with malic acid. If necessary, patients were encouraged to use an alarm clock to ensure that they awoke for the second dose.

During each attended PSG, the sleep-laboratory personnel measured the blood pressure of each patient at bedtime, before the first dose of sodium oxybate, and 4 hours later, before the second dose. A third blood-pressure measurement was made upon arising in the morning.

While undergoing treatment with sodium oxybate, subjects were provided a standard evening meal prior to performing the PSG to reduce variable effects that the presence of food may have on the absorption of sodium oxybate from the gut. In addition, the Epworth Sleepiness Scale (ESS) and a narcolepsy symptom questionnaire were administered during the evening of each clinic visit to obtain subjective measures of daytime sleepiness and the incidence of other narcolepsy symptoms. At each clinic visit, patients were asked to rank the severity of their narcolepsy symptoms compared to symptom severity prior to enrolling in the trial. Specifically, they were asked to rank changes in cataplexy, hypnagogic hallucinations, sleep paralysis, daytime sleep attacks, nighttime awakenings, nighttime sleepiness, nighttime sleep quality, ability to concentrate, and overall condition.

**PSG Recordings**

The PSG data were scored using previously described methods. The PSG data were examined at each site following the initial PSG to exclude subjects with an apnea index greater than 10 events per hour or an apnea-hypopnea index greater than 15 events per hour. The PSG data from each of the 4 study sites were later transferred to a centralized scoring location where the data were uniformly formatted and manually scored by a highly trained registered polysomnographer in a blind manner using a validated software program (Digital Sleep, Inc., Palo Alto, Calif). The following variables were measured in each half of the night and for the entire night according to American Sleep Disorders Association guidelines: sleep latency; total sleep time; duration of stages 1, 2, 3, 4, and rapid eye movement (REM) sleep; REM-sleep latency; and total number of awakenings during sleep. REM density was also determined and defined as the percentage of 2-second REM epochs containing 1 or more REM. Due to controversy regarding the scoring parameters of an arousal and their true significance, arousals were not scored.

The electroencephalogram during non-REM (NREM) stages 1 to 4 in each half of the night was subjected to fast Fourier transformations. Transformations were performed on 5-second nonoverlapping segments of the NREM EEG (C3 - A2) using a Hamming window. All 5-second epochs that, upon visual examination, contained an artifact that distorted the frequency charac-
teristics of the EEG were discarded before the fast Fourier trans-
formations were performed. Because the duration of NREM sleep varies from night to night, computations of the fast Fourier transformations were normalized with respect to time to enable meaningful comparisons between patients and within patients across the dose of sodium oxybate. Specifically, for each subject on a given night, the total delta power in each of the 5-second epochs of NREM sleep was summed and then divided by the total number of 5-second epochs spent in NREM sleep. Delta power was defined as the accumulated EEG signal power for all fre-
quencies between 0.5 Hz and 4 Hz inclusive.

The MWT

The MWT measured the latency to sleep onset during the day when subjects tried to stay awake on their customary dose of stimulant medication. While the MWT was not designed to monitor the frequency of sleep-onset REM periods (SOREMP), these were scored when they occurred. Each patient underwent 4 MWT spaced 2 hours apart, beginning 3 hours after the end of the overnight PSG recording. For each MWT, subjects were placed in a semirecumbent position in a dimly lit room and were instructed to remain awake. Each test was terminated after 40 minutes of wakefulness or after 10 minutes of sleep if the onset of sleep occurred within 40 minutes. Sleep onset was defined as 3 consecutive 30-second epochs of stage 1 sleep or a single 30-second epoch of any other sleep stage. A SOREMP was defined as the occurrence of REM sleep within 10 minutes of sleep onset. Subjects received a standard breakfast before the first MWT and a standard lunch after the second MWT test. Coffee was limited to a maximum of 3 cups on each MWT study day and was consumed at the same time in relation to the 4 tests. Subjects were allowed to smoke but were required to maintain the same sched-
ule on each of the MWT study days.

Statistical Analysis

Data obtained from the PSG, ESS, and MWT were analyzed using a 2-way analysis of variance (ANOVA) with patient and dose group as the main effects. For each analysis, if ANOVA revealed a statistically significant difference among the dose groups, a pair-wise comparison using the least significant differ-
test was performed. If the assumptions of these analyses did not appear to be satisfied, the rank changes from baseline were analyzed using the ANOVA model. The assumptions underlying the ANOVA were verified by evaluating the data for the variable normality of distribution and checking for equality of vari-
ance of the residuals. In addition, the significance of the mean change from baseline (Visit 2a) relative to each dose group was determined using either Student paired t test or Wilcoxon signed rank test. Two-sided P values were reported. Any comparison to baseline that yielded P < .05 was subsequently analyzed between dose groups (Visits 2b, 3, 4, 5, and 6). As this was a pilot study and not statistically powered, the reported levels of significance should be interpreted cautiously.

Ethics

Approval for the study was obtained from the institutional review board at all 4 study sites. This trial was conducted according to the ethical principles of the Declaration of Helsinki. These procedures are in compliance with the United States Code of Federal Regulations and Canadian Regulations. Informed con-
sent was obtained from each subject before starting the trial.

RESULTS

The study was performed with 25 subjects (7 men and 18 women) at 4 clinical trial sites. The subjects had a mean age of 52.6 ± 8.8 years, a mean weight of 84.2 ± 16.4 kg and a mean height of 166.9 ± 8.3 cm; 23 subjects were Caucasian and 2 were African American. Four subjects failed to complete the trial: 1 subject withdrew consent and 1 did not return for the final visit; 2 subjects withdrew from the trial because of adverse events.

All subjects successfully withdrew from antidepressant medica-
tions during the initial 2 weeks of the trial and thus were free of these drugs during the subsequent 2-week baseline period. The most commonly used antidepressants were venlafaxine, fluoxetine, and sertraline. The most commonly used stimulants were modafinil, dextroamphetamine, and methylphenidate, although 4 of the subjects were not using any stimulants. Three subjects were accepted into the trial even though they had not been using antidepressants during the 3 weeks preceding Visit 1.

Effect of Sodium Oxybate on Polysomnographic Variables

Nocturnal Sleep Latency

With the exception of the first treatment night at the 4.5-gram dose, the nightly administration of sodium oxybate resulted in small but significant increases in sleep latency in both halves of the night as a whole at Visit 3 following 4 weeks of nightly treatment with 4.5 g of sodium oxybate (Table 1). Otherwise, no dose-related changes in total sleep time were observed despite increasing the dose of sodium oxybate to 9.0 g per night.

Total Sleep Time

A significant decrease in total sleep time compared to baseline was found during the first half of the night and for the night as a whole at Visit 3 following 4 weeks of nightly treatment with 4.5 g of sodium oxybate (Table 1). Otherwise, no dose-related changes in total sleep time were observed despite increasing the dose of sodium oxybate to 9.0 g per night.

Nocturnal Awakenings

Fours weeks after the withdrawal of antidepressant medica-
tions, no significant change in the number of nocturnal awaken-
ings was noted (Visit 2a). Compared to baseline, the administra-
tion of sodium oxybate significantly decreased the total number of nocturnal awakenings during both halves of the night at night-
ly doses of 7.5 and 9 g (Table 1).

Stage 1 and 2 Sleep

Withdrawal from antidepressant medication (Visit 1) resulted in a significant decrease in the duration of stage 1 sleep 4 weeks later at baseline (Visit 2a). Stage 1 sleep was significantly decreased even further by the administration of sodium oxybate on the first night of treatment (Visit 2b) compared to baseline (Table 1); however, this effect was not observed during any sub-
sequent overnight PSG. Withdrawal of antidepressant drugs at Visit 1 had no significant effect on the duration of Stage 2 sleep at baseline (Table 1). Sodium oxybate administration produced
small and inconsistent changes in the duration of Stage 2 sleep, but none of these changes were significant.

**Stages 3 and 4 Sleep**

Withdrawal of hypnotic and antidepressant drugs (Visit 1) had no significant effect on the duration of slow-wave sleep 4 weeks later at baseline (Visit 2a; see Table 1). Compared to baseline, the duration of stages 3 and 4 (slow-wave) sleep increased in a dose-related manner during each half of the night. This increase became significant during the second half of the night at the 7.5- and 9.0-g doses and for the entire night at the 9.0-g dose. Between-group comparisons revealed a consistent trend for slow-wave sleep to increase with increasing doses of sodium oxybate.

**REM-Sleep Latency and Duration**

Following the withdrawal of antidepressants, the mean REM-sleep latency was significantly reduced to 44.0 minutes during the first half of the night (Visit 2a; see Table 1). This was significantly reduced further to 25.9 minutes following the initial dose of sodium oxybate (Visit 2b). This effect was less evident in the second half of the night. On subsequent nights, increasing doses of sodium oxybate had no consistent effect on REM sleep latency.

During the baseline period, the withdrawal of antidepressant drugs led to a significant increase in the duration of REM sleep during each half of the night. The first night of sodium oxybate administration (Visit 2b) resulted in a significant increase in the total duration of REM sleep during the night, with most of the increase occurring following the first 2.25-g dose (Table 1). However, during all subsequent PSG, there was a decrease in REM sleep, which was significant during the second half of the night and for the night as a whole. Between-group comparisons revealed that REM-sleep time during the second half of the night at the 9-g dose was significantly less than that observed at the 4.5- or 6.0-g doses, suggesting that REM sleep decreased in a dose-related manner.

**Delta Power**

The withdrawal of hypnotics and antidepressants had no significant effect on delta power at baseline; however, on the first night of sodium oxybate administration (Visit 2b), there was a

| Table 1—Changes in Sleep Parameters Following Sodium-Oxybate Administration |

<table>
<thead>
<tr>
<th>Polysomnographic Parameter</th>
<th>Half night of study</th>
<th>1</th>
<th>2a</th>
<th>2b</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean nocturnal sleep latency, min</td>
<td>First</td>
<td>5.6*</td>
<td>2.2</td>
<td>2.3</td>
<td>3.6*</td>
<td>6.3*</td>
<td>4.8***</td>
<td>6.1**</td>
</tr>
<tr>
<td>Mean stage 3/4 sleep duration, min</td>
<td>First</td>
<td>3.9</td>
<td>3.0</td>
<td>7.9</td>
<td>3.5</td>
<td>5.5</td>
<td>9.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Mean REM-sleep latency, min</td>
<td>First</td>
<td>104.5*</td>
<td>44.0</td>
<td>25.9*</td>
<td>43.5</td>
<td>46.6</td>
<td>51.0</td>
<td>77.6</td>
</tr>
<tr>
<td>Mean REM-sleep duration, min</td>
<td>First</td>
<td>17.5*</td>
<td>31.2</td>
<td>43.5*</td>
<td>29.7</td>
<td>26.3</td>
<td>31.3</td>
<td>22.9</td>
</tr>
<tr>
<td>Mean delta power, µV^2/Hz</td>
<td>Total</td>
<td>73125.9</td>
<td>69708.6</td>
<td>82190.9***</td>
<td>74479.9</td>
<td>82307.5*</td>
<td>91917.4***</td>
<td>102337.9***</td>
</tr>
<tr>
<td>Median REM density</td>
<td>First</td>
<td>23.0</td>
<td>22.9</td>
<td>28.3</td>
<td>26.0</td>
<td>24.9</td>
<td>25.1</td>
<td>22.2**</td>
</tr>
<tr>
<td>Mean</td>
<td>26.0</td>
<td>29.8</td>
<td>26.9</td>
<td>24.9*</td>
<td>26.5*</td>
<td>25.5*</td>
<td>22.0**</td>
<td></td>
</tr>
</tbody>
</table>

Visit 1, patients on tricyclic antidepressants or selective serotonin reuptake inhibitors for cataplexy; Visit 2a, baseline after 2-week taper and 2-week washout; Visit 2b, first nightly 4.5-g sodium-oxybate dose; Visit 3, 4 weeks of sodium oxybate, 4.5 g nightly; Visit 4, 2 weeks of sodium oxybate, 6.0 g nightly; Visit 5, 2 weeks of sodium oxybate, 7.5 g nightly; Visit 6, 2 weeks of sodium oxybate, 9.0 g nightly. Between-treatment P values derived from analysis of variance on changes from baseline except rapid eye movement (REM) density. Because of the nonnormal distribution of the data, REM density is expressed as medians. REM density was defined as the percentage of 2-second epochs with rapid eye movements during REM sleep. Between-treatment P values derived using sign-rank test on changes from baseline. All comparisons made with baseline values at Visit 2a.

*P < .05; **P < .01; ***P < .005.
statistically significant increase in delta power compared to baseline during each half of the night (Table 1). Although this effect became much less pronounced after 4 weeks of treatment at the same dose (Visit 3), a very robust increase in delta power was observed in both halves of the night and for the night as a whole with subsequent doses. These dose-related increases in delta power were consistently greater during the second half of the night.

Effect of Sodium Oxybate on Narcolepsy Symptoms

The MWT

Following a 4-week treatment period with nightly 4.5 g of sodium oxybate, a significant increase in the mean sleep latency was observed compared to baseline; ie, patients displayed an increased capacity to remain awake during the day. This effect was even greater at the 9-g dose (Table 2). Patients also demonstrated a dose-related reduction in SOREMP. Eleven subjects displayed SOREMP while taking antidepressants, increasing to 18 after antidepressants were discontinued. Following the administration of sodium oxybate for 10 weeks, only 6 patients demonstrated SOREMP (Table 2).

The ESS

Subjects in the current study rated their daytime sleepiness significantly worse 4 weeks after antidepressant drugs were withdrawn. Administration of sodium oxybate was associated with a progressive dose-related improvement in ESS scores, becoming significant after the initial 4 weeks of treatment (Figure 2); at 7.5- and 9-g doses the ESS scores were significantly lower than those obtained during antidepressant use.

Narcolepsy Symptom Assessment

Patients reported dose-related improvements over the course of the 10-week treatment period. At the end of the trial, subjects reported subjective improvement in daytime sleepiness (76%), nighttime sleep quality (81%), ability to concentrate (67%), and overall condition (81%). The effects of administration of sodium oxybate on patient symptoms are described in Table 3.

Periodic Leg Movements

Because patients receiving sodium oxybate for the treatment for narcolepsy have previously been reported to experience periodic leg movements (PLM),13 patients were specifically observed for emergent PLM during the course of the study. At baseline, approximately 40% of patients exhibited PLM. Although 2 patients exhibited a small increase in the number of PLM after 4 weeks of treatment with 4.5 g of sodium oxybate (Visit 3), the administration of sodium oxybate at doses of 4.5 to 9 g nightly did not cause a significant increase in PLM nor was there any evidence of a dose response or any differences between the first and second half of the night.14

Safety

Of the 25 patients who originally enrolled in the trial, 18 reported at least 1 adverse event; 13 patients reported events considered to be related to the study drug; 2 patients discontinued the study due to adverse events, specifically a respiratory disorder and depression at the 4.5- and 7.5-g doses, respectively; none of the reported events were considered serious. Adverse events were recorded using the Coding Symbols for the Thesaurus of Adverse Reactions Terms. The most commonly reported events were (number, percentage): nausea (5, 20%), back pain (3, 12%), anorexia (3, 12%), vomiting (3, 12%), edema (3, 12%), sleep disorder (2, 8%), and somnolence (2, 8%). There were no mean changes in blood pressure or other vital signs, and there were no significant changes in clinical laboratory parameters. One patient demonstrated an electrocardiogram abnormality during the trial.

Table 2—Changes in Sleep Latency during the Maintenance of Wakefulness Test in Patients with Narcolepsy After Nocturnal Administration of Sodium Oxybate

<table>
<thead>
<tr>
<th>MWT Parameter</th>
<th>Visit 1 2a 3 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 21 n = 21 n = 21 n = 20</td>
<td></td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>5.5 4.5 8.2 10.6</td>
</tr>
<tr>
<td>Mean</td>
<td>1.0 (5.7) — 3.7 (7.7)* 6.1 (6.8)**</td>
</tr>
<tr>
<td>Change from baseline (SD)</td>
<td></td>
</tr>
<tr>
<td>Sleep-onset REM period, no (%)</td>
<td>Yes (52) 18 (86) 13 (62) 6 (30)</td>
</tr>
<tr>
<td>No (48) 3 (14) 8 (38) 14 (70)</td>
<td></td>
</tr>
</tbody>
</table>

Visit 1, patients on tricyclic antidepressants or selective serotonin reuptake inhibitors for cataplexy; Visit 2a, baseline after 2-week taper and 2-week washout; Visit 3, 4 weeks of sodium oxybate, 4.5 g nightly; Visit 6, 2 weeks of sodium oxybate, 9.0 g nightly. Between-treatment P values derived from analysis of variance on changes from baseline. MWT refers to Maintenance of Wakefulness Test; REM, rapid eye movement.

*P < .05; **P < .001.

Figure 2—Changes in Epworth Sleepiness Scale scores by sodium-oxybate dose. Improvements in the Epworth Sleepiness Scale score became significant following 4 weeks of sodium-oxybate therapy at the 4.5-g dose. *Denotes P < .001 vs baseline; n = 21; ACT refers to anticitaplectic therapy.
however, it was determined to be related to an old inferior myocardial infarction and was not considered to be clinically significant.

**DISCUSSION**

The nightly administration of sodium oxybate to patients with narcolepsy resulted in 3 major effects: an initial induction and prolongation of REM sleep followed by a subsequent reduction of this sleep state, an increase in slow-wave sleep, and an improvement in daytime alertness despite the inability of sodium oxybate to increase total nocturnal sleep time.

**Table 3—Subjective Reports of Narcolepsy Symptoms After the Nocturnal Administration of Sodium Oxybate**

<table>
<thead>
<tr>
<th>Symptom, no. (%)</th>
<th>2a n = 21</th>
<th>3 n = 21</th>
<th>Visit 4 n = 21</th>
<th>5 n = 21</th>
<th>6 n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataplexy attacks</td>
<td>Increased</td>
<td>13 (62)</td>
<td>3 (14)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>0 (0)</td>
<td>11 (52)</td>
<td>17 (81)</td>
<td>18 (86)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>8 (38)</td>
<td>7 (33)</td>
<td>4 (19)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hypnagogic hallucinations</td>
<td>Increased</td>
<td>8 (38)</td>
<td>3 (14)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>0 (0)</td>
<td>6 (29)</td>
<td>10 (48)</td>
<td>15 (71)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>13 (62)</td>
<td>12 (57)</td>
<td>10 (48)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>Increased</td>
<td>8 (38)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>0 (0)</td>
<td>8 (38)</td>
<td>14 (67)</td>
<td>15 (71)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>13 (62)</td>
<td>12 (57)</td>
<td>7 (33)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Daytime sleep attacks</td>
<td>Increased</td>
<td>13 (62)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>0 (0)</td>
<td>11 (52)</td>
<td>16 (76)</td>
<td>16 (76)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>8 (38)</td>
<td>9 (43)</td>
<td>5 (24)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>Increased</td>
<td>8 (38)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>3 (14)</td>
<td>11 (52)</td>
<td>11 (52)</td>
<td>13 (62)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>10 (48)</td>
<td>8 (38)</td>
<td>9 (43)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Daytime Sleepiness</td>
<td>Increased</td>
<td>12 (57)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>0 (0)</td>
<td>14 (67)</td>
<td>14 (67)</td>
<td>14 (67)</td>
</tr>
<tr>
<td></td>
<td>Remained the Same</td>
<td>9 (43)</td>
<td>6 (29)</td>
<td>6 (29)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Nighttime sleep quality</td>
<td>Much Improved</td>
<td>0 (0)</td>
<td>4 (19)</td>
<td>5 (24)</td>
<td>5 (24)</td>
</tr>
<tr>
<td></td>
<td>Somewhat Improved</td>
<td>3 (14)</td>
<td>12 (57)</td>
<td>14 (67)</td>
<td>13 (62)</td>
</tr>
<tr>
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<td>4 (19)</td>
<td>2 (10)</td>
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<tr>
<td></td>
<td>Somewhat Worse</td>
<td>4 (19)</td>
<td>1 (5)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td></td>
<td>Much Worse</td>
<td>5 (24)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ability to concentrate</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (14)</td>
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</tr>
<tr>
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<td>9 (43)</td>
<td>10 (48)</td>
<td>11 (52)</td>
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<tr>
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<td>9 (43)</td>
<td>7 (33)</td>
<td>6 (29)</td>
</tr>
<tr>
<td></td>
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<td>9 (43)</td>
<td>3 (14)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Much Worse</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Overall condition</td>
<td>Much Improved</td>
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<td>1 (5)</td>
<td>5 (24)</td>
<td>7 (33)</td>
</tr>
<tr>
<td></td>
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<td>0 (0)</td>
<td>16 (76)</td>
<td>12 (57)</td>
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<tr>
<td></td>
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<td>4 (19)</td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>Somewhat Worse</td>
<td>8 (38)</td>
<td>1 (5)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td></td>
<td>Much Worse</td>
<td>8 (38)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</table>

The number of patients reported does not equal the total patients treated if data were missing. Visit 2a, baseline after 2-week taper and 2-week washout; Visit 3, 4 weeks of sodium oxybate, 4.5 g nightly; Visit 4, 2 weeks of sodium oxybate, 6.0 g nightly; Visit 5, 2 weeks of sodium oxybate, 7.5 g nightly; Visit 6, 2 weeks of sodium oxybate, 9.0 g nightly.

**Effects on REM Sleep**

Four weeks following the withdrawal of hypnotic and antidepressant drugs, an initial 2.25-g dose of sodium oxybate taken at bedtime further reduced the already shortened REM-sleep latency noted at baseline and increased the overall duration of REM sleep during the 4 hours that followed. The second 2.25-g dose of sodium oxybate that same night had no effect on either of these REM variables. After 4 weeks of continuous treatment at this dose, the 2 nightly 2.25-g doses no longer altered REM-sleep latency, although the second dose significantly decreased REM-sleep duration. Reduction of REM sleep and of rapid eye movements during REM sleep became more evident as the total night-
ly dose of sodium oxybate was further increased from 6.0 to 9.0 g and was most pronounced during the second half of the night. The decrease in REM-sleep duration was balanced by increases in NREM stages 2, 3, and 4. At the highest doses, there was a significant increase in NREM stages 3 and 4 (slow-wave sleep). This was most evident in the second half of the night. The greater effects of sodium oxybate during the second half of the night may be related to the higher plasma concentrations of the drug, which typically occur during this time. 15 Although the number of nocturnal awakenings declined significantly as the sodium oxybate dose was increased from 4.5 to 9.0 g, the total sleep time was not increased.

In the current study, sodium oxybate initially further reduced the already short REM-sleep latency observed during the baseline and significantly increased the duration of REM sleep. Previous investigators have also reported that sodium oxybate decreases REM-sleep latency in patients with 1–13, and without16 narcolepsy. Similarly, prolonged periods of REM sleep following sodium-oxybate administration have previously been reported16 but, in our study, were not seen following the first night. The simplest explanation for this observation may be that the pressure for REM sleep had largely been relieved during the previous 4-week withdrawal from REM-suppressing antidepressants.

It is also important to note that sodium oxybate appears to promote normal muscle atonia during REM sleep. The H reflex, a measure of peripheral motor reflex inhibition, cannot be elicited during REM sleep,17 and sodium oxybate similarly inhibits this reflex response.18 In addition, REM rebound does not occur following abrupt discontinuation of sodium-oxybate therapy.16 Thus, with respect to REM sleep, sodium oxybate appears to have effects that extend far beyond those of other sedative hypnotics.

**Effects on Slow-Wave Sleep**

The administration of sodium oxybate was associated with significant changes in slow-wave sleep. Visually, it was apparent that sodium oxybate increases the prevalence and amplitude of EEG slow waves. Moreover, power spectrum analysis reveals a significant increase in delta power at the 2.25-g dose, even before this effect is visually apparent. This increase in slow-wave activity occurs in all sleep stages, including REM sleep. Sodium oxybate failed to increase stages 3 and 4 sleep in normal subjects;19 however, the nocturnal administration of sodium oxybate has consistently been shown to increase slow-wave sleep in patients with narcolepsy.14,16,20 This effect, together with the significant decrease in nocturnal awakenings, may be responsible for the improvements in excessive daytime sleepiness. Although the increase in slow-wave sleep persisted until the end of the 10-week trial, it remains to be determined whether these effects are time or dose dependent.

**Effects on Daytime Sleepiness**

The current study provides additional objective evidence that the nocturnal administration of sodium oxybate is associated with improvements in excessive daytime sleepiness, as there was a significant decrease in subjective and objective measures of daytime drowsiness, in agreement with similar findings reported elsewhere.1,15 Sodium oxybate demonstrated dose-related improvements in the capacity to stay awake during the day and in the subjective sense of alertness. Indeed, at the highest 9-g dose, 6 subjects rated their sleepiness in the normal range (ESS score < 11.0). Such low scores were not found in any of our subjects before treatment with sodium oxybate, despite stimulant therapy in most subjects, and are consistent with the results of a previous sodium-oxybate trial. In that study, sodium oxybate augmented levels of alertness beyond those achieved with stimulants alone and reduced daytime sleepiness to levels observed in the normal population in more than 25% of the trial subjects taking nightly doses of 6 to 9 g.5

It is unclear how increase in alertness occurs because sodium oxybate did not increase the total nocturnal sleep time. Thus, improvements in daytime sleepiness may be related to sleep intensity, generally considered a reflection of slow-wave sleep.21 For example, compensation for sleep loss following sleep deprivation is mediated by an increase in slow-wave sleep to a much greater extent than by an increase in sleep duration.21 Similarly, the increase in slow-wave activity induced by sodium oxybate may elicit the restorative effects of this sleep-intensity mechanism. Although it remains to be demonstrated that the high-voltage slow waves produced by sodium oxybate are similar in nature to the slow delta waves of natural sleep, there is preliminary evidence that both types of slow-wave activity share important physiologic properties.

**CONCLUSION**

The current study represents additional objective evidence that the nocturnal administration of sodium oxybate is associated with improvements in excessive daytime sleepiness. While the lack of a control group and a dosing paradigm that fails to distinguish whether the beneficial effects of sodium oxybate are time or dose dependent are obvious shortcomings in this pilot study, these results suggest that the observed improvement in narcolepsy symptoms are related to changes in sleep architecture. In addition, the results of this study extend the current safety profile of sodium oxybate. Based upon the encouraging results of this study, a much larger placebo-controlled study is being conducted that may shed further light on the actions of sodium oxybate for the treatment of narcolepsy.

**Acknowledgements**

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**REFERENCES**