A 12-month, Open-Label, Multicenter Extension Trial of Orally Administered Sodium Oxybate for the Treatment of Narcolepsy

U.S. Xyrem® Multicenter Study Group

**Objectives:** To evaluate the long-term safety and efficacy of nightly sodium oxybate for the treatment of narcolepsy.

**Design:** A multicenter, 12-month, open-label trial.

**Participants:** 118 narcolepsy patients previously enrolled in a 4-week double-blind sodium oxybate trial.

**Interventions:** Patients were administered 6 g sodium oxybate nightly, taken in equally divided doses at bedtime and 2.5 to 4 hours later. The study protocol permitted the dose to be increased or decreased in 1.5-g increments at 2-week intervals based on efficacy response or adverse experiences but staying within the range of 3 to 9 g nightly.

**Measures:** Narcolepsy symptoms and adverse events were recorded in daily diaries. Safety measures included physical and laboratory examinations repeated at 6 and 12 months. The primary efficacy measure was the change in weekly cataplexy attacks from baseline. Secondary measures included daytime sleepiness using the Epworth Sleepiness Scale (ESS), inadvertent naps/sleep attacks, nighttime awakenings, and the overall change in disease severity as rated by the investigators (Clinical Global Impression of Change; CGI-c).

**Results:** Sodium oxybate, in doses of 3 to 9 g nightly, produced overall improvements in narcolepsy symptoms, which were significant at 4 weeks and maximal after 8 weeks. Reported improvements included a significant decrease in frequency of cataplexy attacks (p < 0.001); diminished daytime sleepiness (p < 0.001); and patient descriptions of nocturnal sleep quality, level of alertness, and ability to concentrate (for each p < 0.001). Adverse events were generally mild and patients showed no evidence of tolerance.

**Conclusion:** Sodium oxybate is an effective and well-tolerated treatment for narcolepsy.

**Keywords:** Narcolepsy, cataplexy, sodium oxybate, gamma-hydroxybutyrate

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**INTRODUCTION**

**NARCOLEPSY IS A CHRONIC, DEBILITATING CENTRAL NERVOUS SYSTEM ILLNESS.** In its classic form it is characterized by excessive daytime sleepiness, inadvertent naps or sleep attacks, fragmented or disturbed nighttime sleep, cataplexy, sleep paralysis, and hypnagogic hallucinations. These symptoms can be very disruptive for the narcoleptic, often leading to an increased incidence of accidents, poor interpersonal relationships, and a generally diminished quality of life. Narcolepsy is estimated to affect 140,000 people in the United States.

The primary cause remains unknown; however, recent human and animal data have suggested that the pathophysiology of narcolepsy involves the neuropeptide hypocretin (orexin). The cell bodies of hypocretin-containing neurons are found in the dorsal, lateral, and posterior hypothalamus where they project to various parts of the brain, particularly nuclei involved in the regulation of sleep and wakefulness. In animals, disruption of hypocretin neurotransmission, at either the neurotransmitter or receptor level, results in the clinical presentation of narcolepsy. In addition, hypocretin was undetectable in the cerebrospinal fluid in 37 of 42 (88%) of patients with narcolepsy, and an 85% to 95% decrease in hypocretin-containing cells has been demonstrated in the postmortem examination of brains from narcoleptic patients.

The possible therapeutic properties of sodium oxybate (gamma-hydroxybutyrate; GHB) in humans were first suggested 40 years ago. Since then, numerous studies have explored the potential clinical uses of sodium oxybate, including the treatment of narcolepsy. These studies demonstrated that sodium oxybate produces clinical improvement in cataplexy and other symptoms related to narcolepsy. These results have also established an acceptable safety profile with a lack of tolerance when used long-term for the treatment of narcolepsy.

Recently, a prospective, randomized, double-blind, parallel-group, multicenter trial revealed that 6 g and 9 g of sodium oxybate, taken in divided doses immediately before bedtime and repeated 2.5 to 4 hours later, produced significant clinical improvement of narcolepsy symptoms. At nightly doses of 6 g and 9 g, statistically significant improvements were seen in the reported number of weekly cataplexy attacks and inadvertent daytime naps. At the 9 g dose, there were also significant improvements in nocturnal awakenings, daytime sleepiness, and the overall investigator assessment of disease severity. This 4-week study found sodium oxybate to be generally well tolerated. The present study is an open-label, long-term, multicenter extension of the above trial.

**Study Objectives**

The objectives of this study were to evaluate the safety and efficacy of sodium oxybate when administered in narcoleptic patients for 12 months at doses of 3, 4.5, 6, 7.5, or 9 g nightly. Protocol amendments allowed patients to continue the study for up to 24 months. Measures of safety included adverse experiences, clinical laboratory analyses, vital signs, and general physical examination. Measurements of efficacy included reports of the change in frequency of cataplexy attacks, Epworth Sleepiness Scale, and patient descriptions of sleep quality, level of alertness, and ability to concentrate.
attacks, daytime sleepiness, frequency and duration of inadvertent naps or sleep attacks, the number of nocturnal sleep awakenings, total amount of sleep, incidence of hypnagogic hallucinations, and sleep paralysis by the study participants in daily diaries. It also included the assessment of change in overall disease severity by the investigators. This assessment was compared to disease severity at baseline following a washout of anticitaplectic medications but while remaining on stable doses of stimulants.

METHODS

Subjects

This study included patients who were 18 years of age or older and expressed a willingness to complete the entire study. Diagnostic criteria included a valid polysomnogram within the previous 5 years and a current diagnosis of narcolepsy for at least 6 months based on criteria established by the American Academy of Sleep Medicine. This study excluded patients who were receiving investigational therapy other than sodium oxybate/placebo in the 30 days prior to the study; diagnosed with sleep apnea or had any other cause of daytime sleepiness; taking hypnotics, anxiolytics, antidepressants, antihistamines, clonidine, or anti-convulsants; at risk of pregnancy; experiencing unstable disease states or disorders that might prevent them from completing the study; at risk of any history of seizure disorder; known to have a history of psychiatric abnormalities; experiencing unstable disease states or disorders that might prevent them from completing the study; at risk of any history of seizure disorder; known to have a history of psychiatric abnormalities; experiencing unstable disease states or disorders that might prevent them from completing the study; at risk of pregnancy; experiencing unstable disease states or disorders that might prevent them from completing the study.

Treatments

Prior to receiving trial medication in the initial 4-week double-blind study, patients discontinued any hypnotic medications and, over a 4-week period, gradually withdrew from all anticitaplectic medications. This was followed by a washout period of 5 days or five times the half-life of the discontinued anticitaplectic medication up to 28 days, whichever was longer. During a subsequent 14 to 21-day baseline period, patients recorded the frequency of cataplectic episodes and other symptoms of narcolepsy in daily patient diaries. A minimum of 3 cataplexy attacks per week during the last 2 weeks of the baseline period were required to enter the double-blind treatment study.

Following a 3 to 5-day washout period of sodium oxybate at the end of the previous double-blind trial, 118 patients elected to enroll in the current 12-month study. Patients began treatment at 6 g of sodium oxybate nightly taken in two equally divided doses. The first dose was taken at bedtime immediately upon retiring and the second dose 2.5 to 4 hours later. Patients were encouraged to use an alarm clock to ensure waking for the second nightly dose of sodium oxybate. Based on clinical efficacy or adverse experiences, the investigator could choose to decrease the total nightly dose to 3 g or 4.5 g or increase it to 7.5 g or 9 g. Dose adjustments were recommended at 2-week intervals in 1.5 g increments. Sodium oxybate was initially dispensed in powder form to be dissolved in water. However, the powder was replaced following the development of a liquid sodium oxybate formulation. These two forms of study medication were determined to be bioequivalent, and no change in patient response to the liquid formulation was noted.

Because of the long-term nature of the trial, it was deemed unethical to withhold stimulant medications. Patients were permitted to continue on stimulant medications but were required to remain on a stable dose throughout the trial. Thus, any improvements in patients’ condition were likely to be due to nightly sodium oxybate therapy. Of the 118 patients initially enrolled in the study, 104 (88.1%) were taking concomitant stimulant medications, consisting of methylphenidate (N=52), amphetamines (N=44), pemoline (N=21), and mazindol (N=1)(some patients were taking more than one type of stimulant drug).

The investigators evaluated patients every 2 weeks during the first month of the study, then every 2 months until month 12. Patients’ vital signs were measured at each clinic visit. The baseline physical and neurological examinations, clinical laboratory tests and ECG were repeated at 6 and 12 months. Compliance with study medication was assessed by comparing the amount of medication remaining at each visit with the amount predicted to remain if the patient were compliant.

Daytime subjective somnolence was assessed using the Epworth Sleepiness Scale (ESS). The overall severity of each patient’s disease was estimated using the Clinical Global Impression of Severity (CGI-s) at baseline and prior to sodium oxybate treatment in the previous blinded study. Subsequent change in disease severity was measured with the Clinical Global Impression of Change (CGI-c) administered at each clinic visit. Possible CGI-c assessments were Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, or Much Worse.

Figure 1—Mean percent change in total number of cataplexy attacks per week following the double-blind trial for all doses. This change was significant for all doses at one month (p < 0.001). This was also true for individual doses except 3 and 4.5 g where the change in cataplexy became significant after 2 months. The variability seen during the first two months of treatment was due to the change in patient doses while undergoing dose titration, which diminished as the study proceeded.

![Figure 1](image)

Table 1—Number of patients in each sodium oxybate dose group after 12 months of therapy.

<table>
<thead>
<tr>
<th>DOSE</th>
<th>3 g</th>
<th>4.5 g</th>
<th>6 g</th>
<th>7.5 g</th>
<th>9 g</th>
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<td>16</td>
<td>11</td>
<td>42</td>
<td>13</td>
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<tr>
<td>%</td>
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<td>9.4</td>
<td>35.9</td>
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<td>29.9</td>
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Figure 2—Combined median change from baseline Epworth Sleepiness Scale per month for all doses following the double-blind trial. This change was significant after month 1 (* denotes p < 0.001) compared to a median score of 18 prior to entry in the previous 4-week double-blind study.

![Figure 2](image)
During the 12 months of the study, patients recorded clinical response information in personal diaries on a daily basis. The daily patient diaries were the same as those used in the previous blinded study and included detailed descriptions of the symptoms to be recorded should they occur. Patients were instructed on the use of diaries by study coordinators and investigators. Patient diary information collected during the trial included the frequency of cataplexy attacks, number and duration of nocturnal awakenings, total amount of sleep each night, the number of hypnagogic hallucinations, and the incidence of sleep paralysis. In addition, diaries were used to document the occurrence of all adverse events. Patients were encouraged to utilize the daily diary every morning and evening. Thus, daily diary recordings were made in a manner consistent with the previous double-blind trial.

Statistical Analysis

Each patient was assigned to a treatment group by calculating the average dose used over the course of the study and rounding to the nearest dose category, i.e., 3, 4.5, 6, 7.5 or 9 g. Treatment group comparisons were made for the frequency of cataplexy attacks, the primary efficacy measure. These comparisons were based on the analysis of covariance and the use of log transformation of the data prior to analysis when the criteria for normal data distribution were not met. Within-group and all-patient analyses were performed using Wilcoxon sign rank test. For secondary efficacy variables that were continuous measures, ANCOVA was used to examine overall treatment effects. Within-group comparisons were performed using paired t-tests. For dichotomous efficacy measures, Fisher’s exact test was used to examine overall treatment effects. Missing data were excluded from calculations. Patients who discontinued the study were included in all analyses up to the time of their withdrawal. Although patients were permitted to continue the study beyond the originally planned 12 months, only data from the first 12 months of the study were analyzed.

Ethics statement

The Institutional Review Board for each of the 15 trial centers approved the protocol, and written informed consent was obtained from each patient prior to initiation of the study. This study was conducted in accordance with the ethical principles delineated in the Helsinki Declaration of 1975, as revised in 1997.

RESULTS

One hundred eighteen patients were initially enrolled in this study. One patient failed to return diary information and was excluded from the analysis. Of the remaining patients, the mean age was 43.4 years (range 18 - 79); 51 were male and 66 were female; 95 (81.2%) patients completed 3 months of therapy, 87 (74.4%) patients completed 6 months, and 80 (68.4%) patients completed the 12-month protocol. Reasons for failing to complete the study included adverse events (11), refusal of consent (7), noncompliance (5), lost to follow-up (5), and other reasons not directly related to the study, such as geographic relocation (9).

Of the 117 patients included in this open-label extension trial, 86 (73.5%) reached a stabilized dose defined as no change in dose for at least 3 consecutive visits. The mean time to stabilization for these patients was 3.38 weeks. The last reported dose for each patient entered into the study is shown in Table 1.

EFFICACY

Cataplexy

The number of cataplexy events recorded in patient diaries was compared to that recorded at baseline from the 4-week double-blind trial. There was a positive effect across all treatment groups. This effect was significant at one month, decreasing by an average of 23.6 cataplexy attacks per week (p < 0.001), and further declining by an average of 35.48 attacks at the end of the study period. These data are presented in Figure 1 and are expressed as dose groups. No attempts were made to assess the severity of cataplexy attacks during the trial.

Daytime Sleepiness

During the baseline phase of the previous 4-week double-blind trial, the mean score of the ESS was 18. In the present study, there was a significant improvement in daytime sleepiness, adjunctive to that achieved by stimulants alone. This was significant for all treatment groups at 1 month except for the 4.5 g dose group, due to the small number of patients (N = 6). The overall improvement was maximal after 2 months (p < 0.001) and significant across all doses, representing an approximately 30% decrease in mean score. This response was maintained for the remainder of the study period. Data for 12 months, showing the combined median change from baseline ESS scores, are displayed in Figure 2.

Clinical Global Impressions of Change

The CGI-c is a clinical measure based on the clinical investigator’s overall impression of the change in the patient’s condition compared to the Clinical Global Impression of Severity established at baseline. Approximately 80% of patients were determined to have a positive response to treatment after 2 months, being categorized as Much Improved or Very Much Improved by the investigators. This positive response was maintained during the course of the study and is graphically presented in Figure 3.

Other Parameters

Other improvements reported by patients in daily diaries included patient descriptions of nocturnal sleep quality, level of alertness, and ability to concentrate adjunctive to that achieved by stimulants alone (for each
While not reaching statistical significance, there was also a substantial decrease in the number and duration of inadvertent naps or sleep attacks over the course of the study. Compared to baseline values, the change in the total number of daily sleep attacks (SD) was -0.77 (1.28) after 1 month of treatment and -1.03 (1.29) after 12 months; the change in the mean duration of sleep attacks (SD) was -20.27 min (39.0) at 1 month and -29.64 min (47.74) at 12 months. There were similar decreases in the number and duration of planned naps and nighttime awakenings over the course of the study although the total duration of nightly sleep remained unchanged (data not shown).

Among the 102 (87.2%) patients reporting hypnagogic hallucinations and 103 (88.0%) reporting sleep paralysis at baseline, there was a nonsignificant decrease in the frequency of episodes of both phenomena that became evident after 1 month and continued over the duration of the study. The change from baseline (SD) for weekly number of hypnagogic hallucinations was -0.48 (1.83) to -0.78 (2.38) and for weekly number of sleep paralysis episodes -0.38 (0.95) to -0.51 (1.29).

SAFETY

Adverse event terms used in this report are based on the Coding Symbols for the Thesaurus of Adverse Reactions Terms (COSTART). Event descriptions supplied by the investigators were categorized by body system and by preferred COSTART terms. Adverse events of any kind were reported by 109 patients (93.2%) during the 12-month study.

Adverse Events

The most commonly reported adverse events were headache, nausea, viral infection, dizziness, pain, enuresis and somnolence. Of these seven events, only dizziness occurred at a significant level (p < 0.05) for overall treatment group comparisons. Adverse events occurring in at least 10% of patients for any one of the five average doses during the initial 12 months of the study are summarized in Table 2. There were no deaths occurring during the study.

Three patients experienced a serious adverse event during the course of the study. One patient was a 41-year-old male who developed recurrent chest pain. Although his electrocardiogram was normal, the investigator chose to discontinue treatment with sodium oxybate. Subsequently, 26 days after his last dose of sodium oxybate, the patient suffered a mild myocardial infarction and chose not to continue the study. Another patient, a 56-year-old male with a history of breast tumor removal, developed a ductal carcinoma in his left breast requiring surgical removal. This patient continued treatment and completed the 12-month study. The third event occurred in a 76-year-old woman who experienced agitation. This occurred on her first night following an upward titration of her sodium oxybate dosage and after her second nightly dose. She was treated in a local hospital where her physical and laboratory examination were found to be normal and she was discharged to home. Although this event was considered to be possibly related to the medication, she completed the 12-month study without recurrence.

LABORATORY ABNORMALITIES

The majority of endpoint laboratory values remained unchanged at the end of the study. There was a significant change in serum phosphorus (hypophosphatemia; p = 0.023) across dose groups. This change was believed to be due to natural variability as there was no significant change within dose groups. Similarly, there was a significant change in serum calcium (hypocalcemia; p = 0.034). Although these values dropped below the normal range, they were not considered clinically significant and, as these changes were observed only within the 6 g dose group, this effect was believed to be spurious. Only a mild increase in SGPT was determined to be possibly related to the study medication. However, it was considered to be of no clinical significance. No patients discontinued drug therapy because of an adverse laboratory event.

VITAL SIGNS

The only significant change in vital signs was a mild decrease in diastolic blood pressure observed across treatment groups. The maximum decrease observed was 7 mm Hg and was determined to be clinically insignificant.

ADVERSE EVENTS RESULTING IN WITHDRAWAL FROM STUDY

Eleven patients chose to discontinue participation in the study due to an adverse event during the first 12 months of the trial, representing 9.4% of all patients who began the study. The COSTART terms for these events were abnormal coordination, amnesia, apathy, asthenia, decreased libido, depression, dyspnea, hypesthesia, headache, metallic taste, nervousness, pregnancy (protocol violation), psychosis, somnolence, stomach upset, and weight loss (4 patients experienced more than one adverse event). The adverse event “psychosis” represents a single patient who had a previous history of mental illness.

DISCUSSION

Efficacy

The data from this open-label study demonstrate that 3 g to 9 g doses of sodium oxybate, taken nightly in equally divided doses at bedtime and again 2.5 to 4 hours later, produced significant and long-term clinical improvement in the frequency of cataplexy attacks and diminished daytime sleepiness. Clinical improvement was maintained throughout the study. Of the 118 patients who entered the trial, 103 (87%) were taking concomitant stimulant medications, making the adjunctive improvement in daytime sleepiness especially noteworthy.

Clinical improvement trends included decreased frequency and duration of inadvertent naps or sleep attacks and diminished frequency of planned naps, hypnagogic hallucinations, and episodes of sleep paralysis. These improvements did not reach statistical significance, although they did demonstrate a continuous improvement trend for the duration of the 12-month trial.

There was no evidence that tolerance developed to the effects of sodium oxybate. Once a stable dose was achieved, there were few subsequent changes in dose, and substantial clinical efficacy was maintained without dose escalation.

Together, these results confirm and extend the observations of other investigators, and further support the therapeutic role of sodium oxybate for the treatment of cataplexy in patients with narcolepsy.
Safety

Sodium oxybate was generally well tolerated. Adverse events encountered in this study affected primarily the central nervous and digestive systems. There was no dose relationship for the most common adverse events, and the majority were mild to moderate in severity. Only nausea, dizziness, somnolence, headache, and enuresis were considered related to sodium oxybate therapy.

Although several patients who dropped from the study abruptly stopped taking sodium oxybate, there were no reports of adverse events suggestive of either dependence or withdrawal from the study medication. In addition, there was no evidence of dose-escalation, which might suggest tolerance to the therapeutic benefits of sodium oxybate, or any tendency for abuse. Both of these findings are consistent with other long-term human trials with sodium oxybate for the treatment of narcolepsy. They are also consistent with recent reports that sodium oxybate has only very weak reinforcing properties.

In summary, sodium oxybate was reported to produce clinical improvement in narcolepsy symptoms, with a maximal effect seen after 2 months of treatment when administered at doses of 3 g to 9 g nightly. These improvements included decreased frequency of cataplexy attacks, diminished daytime sleepiness, and decreasing trends in the frequency and duration of inadvertent naps, daytime sleep attacks, and decreased frequency of hypnagogic hallucinations and sleep paralysis. Sodium oxybate appears to be well tolerated when used over long periods. These data indicate that sodium oxybate may safely be used in conjunction with central nervous system stimulants and provide further evidence that sodium oxybate is an effective therapy for narcolepsy.

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