A Randomized Trial Evaluating the Effectiveness of Sodium Oxybate Therapy on Quality of Life in Narcolepsy

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Study Objectives: To evaluate the efficacy of sodium oxybate versus placebo to improve quality of life in patients with narcolepsy.

Design: A multicenter, double-blind, placebo-controlled trial.

Setting: Outpatient facility of 42 sleep centers in the United States, Canada, and Europe

Participants: Study participants were 285 patients with narcolepsy, 16 to 75 years of age, with a median Epworth Sleepiness Scale score of 18, a Maintenance of Wakefulness Test sleep latency of 9.56 minutes, and experiencing symptoms of narcolepsy, including cataplexy and excessive daytime sleepiness with recurrent sleep episodes almost daily for at least 3 months at the time of enrollment.

Interventions: Subjects were gradually withdrawn from narcolepsy medications used for cataplexy, including antidepressants. Subsequently, participants were randomly assigned to receive 4.5, 6.0, or 9.0 g per day of sodium oxybate or placebo taken in two equally divided doses upon retiring to bed and again 2.5 to 4 hours later for 4 weeks during the stable dosing phase.

Measurements and Results: The change in quality of life following the administration of sodium oxybate was measured with the Functional Outcomes of Sleep Questionnaire. The nightly administration of sodium oxybate produced significant dose-related improvements in the Total Functional Outcomes of Sleep Questionnaire score, as well as in the Activity Level, General Productivity, Vigilance, and Social Outcomes subscales.

Conclusions: The nocturnal administration of sodium oxybate in patients with narcolepsy was associated with statistically significant and clinically relevant improvements in functional status, an important component of quality of life.

Keywords: Narcolepsy, sodium oxybate, quality of life, functional status, daytime sleepiness, gamma-hydroxybutyrate

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INTRODUCTION

A PREVIOUS STUDY OF PATIENTS WITH NARCOLEPSY DEMONSTRATED THAT THE ADMINISTRATION OF SODIUM OXYBATE RESULTED IN SIGNIFICANT CHANGE in sleep architecture, with increased sleep latency, decreased total sleep time, fewer nocturnal awakenings, increased slow-wave sleep, decreased rapid eye movement sleep, and greater delta power.[1] Moreover, there is evidence that sodium oxybate also decreases daytime sleepiness, with a reduction in sleep-onset rapid eye movement (REM) periods, sleep attacks, hypnagogic hallucinations, and cataplexy.[2-6]

It is likely that these improvements would ameliorate the deficits in daily functioning reported for patients with narcolepsy. Indeed, patients with narcolepsy function in a haze of chronic sleepiness, with difficulty maintaining vitality, social functioning, personal relationships, and leisure activities and executing daily activities.[7,8] Scores on a generic measure of functional status, the SF-36, have demonstrated that patients with narcolepsy not only have lower subscale scores than normal controls for vitality, social functioning, general health perception, physical functioning, mental health, bodily pain, and difficulty performing activities due to physical and emotional problems,[7,9] but their scores are as bad or worse than individuals suffering from obstructive sleep apnea, Parkinson disease, and epilepsy.[8,9] Moreover, employing a disease-specific measure of functional status, the Functional Outcomes of Sleep Questionnaire (FOSQ), Teixeira and colleagues[8] found that patients with narcolepsy had lower scores compared with patients with untreated and treated sleep apnea in the domains of general productivity, social outcomes, and vigilance, as well as global functioning reflected by the Total score.

The effect of sodium oxybate on functional status, a component of quality of life, has not been previously evaluated in patients with narcolepsy. The purpose of this randomized, double-blind, placebo-controlled parallel-group clinical trial in patients diagnosed with narcolepsy included an evaluation of the change in functional status in patients with narcolepsy receiving nightly doses of 4.5, 6.0, or 9.0 g per day of sodium oxybate or placebo. This study is reported in accordance with the CONSORT statement.[10]

Disclosure Statement

This is an industry supported study supported by Orphan Medical, Inc., a subsidiary of Jazz Pharmaceuticals. The trial was conducted by members of the Xyrem® International Study Group. Dr. Weaver served as a consultant on the study. The paper was independently written by Drs. Terri Weaver and Norma Cuellar. Analyses of data were independently performed by a contract research organization that certified the study was conducted in compliance with Good Clinical Practice. Dr. Weaver has received research equipment from Protech and Respironics, Inc.; is a consultant for Sanofi-Aventis Pharmaceutical; has participated in a speaking engagement supported by Cephalon, Inc.; and has received license fees for the Functional Outcomes of Sleep Questionnaire from Jazz Pharmaceutical, Sanofi-Aventis Pharmaceutical, Organon NV, Sleep Solutions, Aspire Medical, and InfluENT Medical. Dr. Cuellar has indicated no financial conflict of interest.

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METHODS

Study Design and Objectives

The objective of this multicenter, randomized, placebo-controlled trial, conducted by the members of the Xyrem® International Study Group, was to evaluate the efficacy and safety of sodium oxybate oral solution, compared with placebo, for the treatment of narcolepsy. The study was specifically designed to test the hypothesis that active treatment with sodium oxybate is more effective than placebo for treating excessive daytime sleepiness in patients with narcolepsy. This paper reports the results from this study demonstrating the impact of sodium oxybate versus placebo on functional status. The results for the primary outcome, daytime sleepiness, have been previously reported,[4] and the reader is referred to that paper for a description of the study methodology.

Participants

Patients diagnosed with narcolepsy according to American Academy of Sleep Medicine criteria,[11] documented by overnight polysomnogram and Multiple Sleep Latency Test performed in the last 5 years, were included in the study if they met the previously described study criteria.[4] In summary, participants were at least 16 years of age; had current symptoms of narcolepsy, including excessive daytime sleepiness, cataplexy, and recurrent sleep attacks almost daily for at least 3 months; had not participated in a clinical trial of an investigational therapy in the last 30 days; did not have another sleep disorder; had no recurrent use of hypnotics or sedating medication; had a history of stable medical and psychiatric illness; and did not engage in an occupation requiring variable shift work or routine night shifts. Women of childbearing potential were required to use a medically accepted method of birth control unless surgically sterile or 2 years postmenopause. Participants refrained from operating a motor vehicle or machinery if indicated by the investigator.

Participants were recruited from the sleep medicine practices of the participating centers. All participants provided written informed consent, and the protocol was approved by the Institutional Review Board at each clinical center. All data were collected at the outpatient facility of the clinical center according to the visit schedule.[4]

Interventions

The active agent, as previously described,[4] was a liquid solution containing sodium oxybate at a concentration of 500 mg per mL. The placebo agent was an equimolar solution of sodium citrate, the taste of which was indistinguishable from the active agent (Orphan Medical, Inc., unpublished data). Both agents were measured into two, equally divided doses each night using an oral dispensing device and diluting with 2 ounces of water. Participants were instructed to prepare each dose prior to bed and to take the first dose while in bed, immediately before going to sleep, and the second dose 2.5 to 4 hours later. Participants were advised to use an alarm clock to awaken them for the second dose.

The study consisted of 5 to 7 visits over an 18-week period. The first 14 days (Visits 1-2) were the lead-in period, followed by a 21-day withdrawal from anticataplectic therapy (Visits 2-3). This was followed by a 5- to 18-day washout period (Visit 3), concluding with randomization to the two treatment arms and doses of 4.5, 6, or 9 g per day of study medication (Visit 4). Baseline data were then collected for the next 14 to 21 days (Visit 5). Participants then received 7 days of 4.5 g per day sodium oxybate or placebo (Visit 5), followed by titration to their final dose according to the randomization scheme (Visits 6 and 7). Participants assigned to active treatment were on study medication for at least 7 days before proceeding to the next dose (see reference 4 for further description of activities during each visit and the dose-titration phase). The FOSQ was administered during Visits 2, 5, 6, and 7.

Blinding

As indicated above, only the participants were blinded during visits prior to the collection of baseline data (Visit 5), with the remainder of the study being double-blinded, ie, the participant, site investigator, those dispensing the medication, and those administering instruments were blinded to treatment allocation. Blinding was accomplished as follows: a scratch-off blinding label was affixed to each container of investigational medication. The label was removed and placed on the participant's dispensing record. Authorization to break the blind was provided only in case of an emergency and provided only to the investigator and medical monitor of Orphan Medical. No blinds were broken during the trial.

Outcomes

Daily diaries were used by participants to record narcolepsy symptoms, adherence to trial medication, concomitant medication use, and occurrence of sleep paralysis and hypnagogic hallucinations, as well as adverse experiences. Additional outcomes measures included the Epworth Sleepiness Scale, SF-36 (a generic measure of health status), the FOSQ, Clinical Global Impression of Change scale, nocturnal polysomnography, and the Maintenance of Wakefulness Test. This paper will only report on results of the assessment of functional status, a secondary endpoint, measured with the FOSQ. Other results are reported elsewhere.[4,12]

The FOSQ, a disease-specific measure of functional status, a component of quality of life, is a 30-item Likert-style questionnaire that examines the impact of being sleepy or tired on the ability to conduct daily activities.[13] This measure contains 5 subscales: Activity Level, Vigilance, Intimacy and Sexual Relationships, General Productivity, and Social Outcome. It has established content validity, concurrent validity with other functional status instruments, test-retest reliability ($r = 0.91$), discriminant validity between patients with obstructive sleep apnea and normal subjects, and internal consistency ($\alpha = 0.96$). A Total score is generated from the calculation of the mean item scores for each subscale. The Total Score ranges from 5 to 20, with subscale scores ranging from 1-4.

Data quality was ensured with initial in-depth training of study-site personnel, on-site visits with monitoring of case report forms, and double entry of all data, with oversight by a third-party referee.

Statistical Methods

The sample characteristics were evaluated using summary sta-

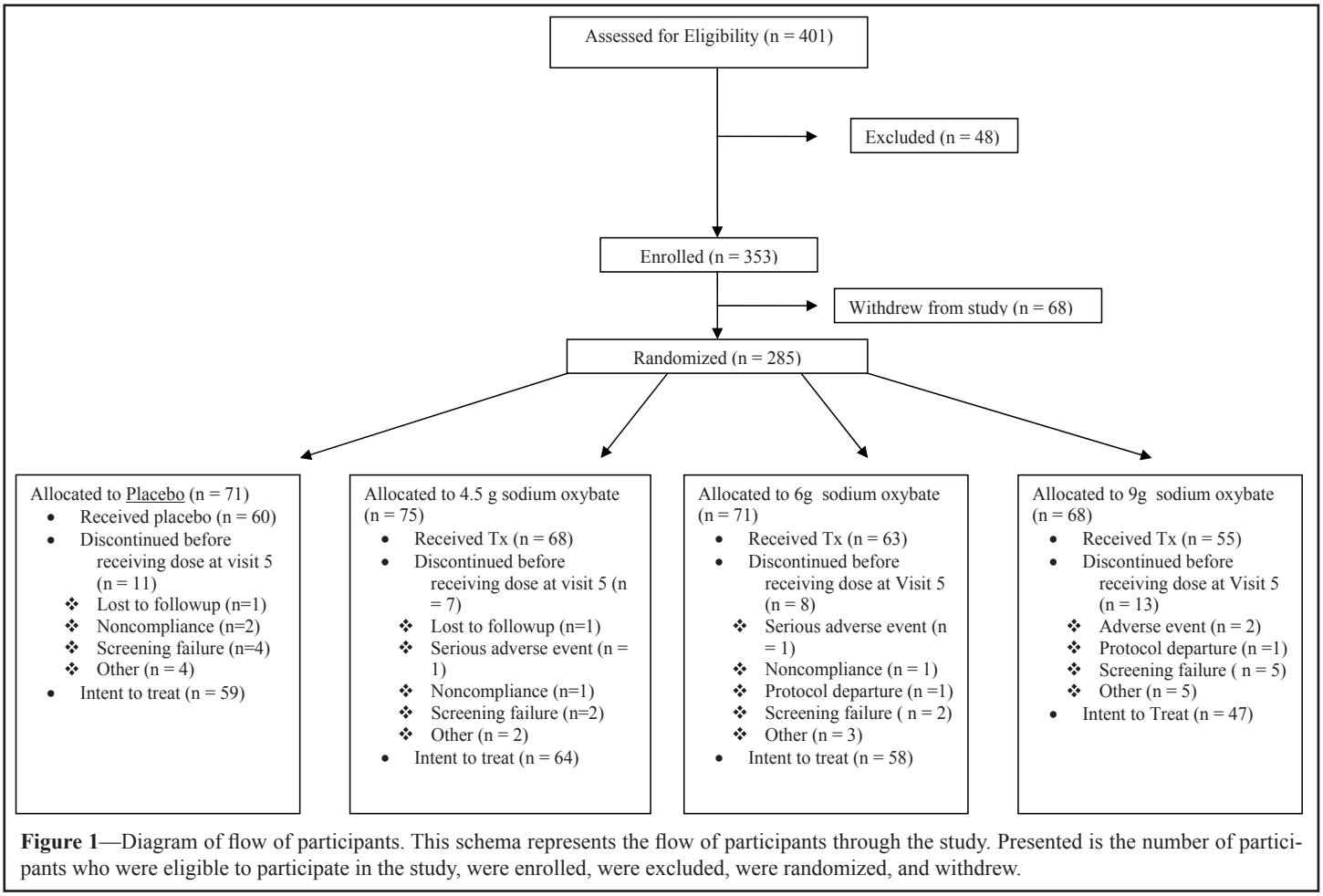

Figure 1—Diagram of flow of participants. This schema represents the flow of participants through the study. Presented is the number of participants who were eligible to participate in the study, were enrolled, were excluded, were randomized, and withdrew.

tistics with values given as mean + SD, medians, and ranges or proportions, as appropriate. The analyses, change from baseline (Visit 5) in FOSQ Total and subscale scores at Visits 6 or 7 were carried out on the intent-to-treat population, defined as those participants who received 1 or more doses of double-blind trial medication who were randomized at Visit 4 and for whom baseline and any postbaseline efficacy measurements were available. If data were unavailable for a participant, the last observation carried forward technique was used with the last postbaseline observation available for the participant. Because the data did not meet the assumptions of normality and homogeneity of variance, the Kruskal-Wallis test, with Bonferroni adjustment, was employed to examine differences between groups and interventions instead of the planned analysis of variance. The significance of the mean change from baseline within each treatment group was determined using pairwise comparisons applying the Mann-Whitney test and considered significant for $p < .0167$ with the Bonferroni adjustment. Effect sizes for each active-treatment group compared with placebo were calculated for the FOSQ scores using Cohen's d measure for two independent samples.[14] The number of participants' data that were analyzed for each treatment group is depicted in Figure 1.

The sample-size calculations were based on the primary endpoint for the study, the change in daytime sleepiness measured by the Epworth Sleepiness Scale, and the investigator's clinical global assessment. The sample-size calculation was based on a power of 90% (80% for each variable with Bonferroni adjustment and 2-tailed significance level of .05). Assuming a treatment-group difference of 3.5, as demonstrated in a previous trial, it was determined that 25 patients per treatment group world be required. For the Clinical Global Impression-change scale, it was assumed that the success rate (much or very much improved) for placebo would be 30%, whereas the success rate for sodium oxybate oral solution would be 75%. Based on these assumptions, it was determined that 37 patients per treatment group would be required. To allow for a 10% withdrawal rate and some slight departure in the assumptions utilized for the calculations, at least 50 patients would be randomly assigned to each of the four treatment groups: placebo and 4.5, 6.0, and 9.0 g per day of sodium oxybate. No interim analysis was planned or performed. An independent data safety monitoring board was not used in this trial.

RESULTS

As depicted in Figure 1, 401 patients were assessed for eligibility, with 353 enrolled between November 30, 2000, and March 31, 2004. Forty-eight participants did not meet the study criteria and were eliminated; 68 participants withdrew from the study, and the remaining 285 were randomly assigned to placebo (n = 71) or 4.5 (n = 75), 6.0 (n = 71), or 9.0 g per day (n = 68) of sodium oxybate; 246 participants received at least 1 dose of the intervention treatment; 228 participants received at least 1 dose of the double-blind medication and had both baseline (Visit 5) and postbaseline (Visit 6 or 7) efficacy observations and were defined as the intent-to-treat population. The reasons for withdrawing from the study before receiving the intervention at Visit 5 are

Table 1—Participant Characteristics by Treatment Group at Trial Entry[a]

Characteristic	Placebo	Sodium Oxybate			Total
	n = 59	4.5 g, n = 64	6.0 g, n = 58	9.0 g, n = 47	N = 228
Sex					
Men	17 (28.8)	21 (32.8)	22 (37.9)	19 (40.4)	79 (34.6)
Women	42 (71.2)	43 (67.2)	36 (62.1)	28 (59.6)	149 (65.4)
Race					
White	54 (91.5)	50 (78.1)	49 (84.5)	43 (91.5)	196 (86.0)
Black	3 (5.1)	11 (17.2)	7 (12.1)	4 (8.5)	25 (11.0)
Asian	1 (1.7)	1 (1.6)	0	0	2 (0.9)
Hispanic	1 (1.7)	0	1 (1.7)	0	2 (0.9)
Other	0	2 (3.1)	1 (1.7)	0	3 (1.3)
Age, y	40.8 ± 15.5	41.8 ± 16.7	39.2 ± 15.9	39.9 ± 12.5	40.5 ± 15.3
Weight, kg	81.9 ± 19.8	84.1 ± 21.6	90.2 ± 19.8	87.3 ± 18.9	85.7 ± 20.3
Height, cm	167.7± 7.4	167.4 ± 9.4	167.5 ± 10.0	170.2 ± 10.7	168.1 ± 9.4

[a]Intent-to-treat population.
Data are presented as mean ± SD, except sex and races, which are presented as number (%).

Table 2— Change From Baseline in Functional Outcomes of Sleep Questionnaire at Visit 7[a]

FOSQ Scale	Dose of Sodium Oxybate, g					
	6.0			9.0		
	Mean Change	p Value	Effect Size[b]	Mean Change	p Value	Effect Size[b]
Total	1.65 + 1.99	.04	0.44 Small	3.43 + 3.23	< .001[c]	0.99 Large
Activity Level	0.40 + 0.48	.006[c]	0.52 Medium	0.71 + 0.69	< .001[c]	0.96 Large
Vigilance	0.41 + 0.60	.021	0.44 Small	0.83 + 0.86	< .001[c]	0.92 Large
General Productivity	0.35 + 0.48	NS	0.36 Small	0.67 + 0.74	.002[c]	0.80 Large
Social Outcomes	0.45 + 0.67	.011[c]	0.56 Small	0.78 + 0.79	< .001[c]	0.96 Large
Intimacy and Sexual Relationships	0.02 + 0.65	NS	-0.27 Small	0.35 + 0.82	NS	0.26 Small

[a]Intent-to-treat population. FOSQ refers to Functional Outcomes of Sleep Questionnaire.
[b]Effect sizes were calculated for treatment compared to placebo based on Cohen d measure for 2 independent samples.(14)
[c]Significant with Bonferroni adjustment.

listed in Figure 1.

The demographic characteristics are presented in Table 1. The participants were predominantly white (86%) women (65%), median age of 38 years (range 16 – 75 years), and median weight of 83.0 kg (range 46.3 to 170.6 kg). At the time of enrollment, participants experienced a median number of 17 cataplexy attacks per week (range 0-967.50), a median of 19 nocturnal awakenings (range 0-475), 2.04 (range 0-40.10) weekly hypnagogic hallucinations, 1.5 (range 0-40) weekly sleep paralysis episodes, and 16 (0-99.80) inadvertent naps or sleep attacks per week. The average latency on the Maintenance of Wakefulness Test was 12.01 + 9.68 minutes and the Epworth Sleepiness Scale score was 17.8 + 3.68. There were no significant differences between groups in demographic characteristics and narcolepsy symptoms. Considering the 285 participants randomly assigned to intervention, 78% were taking stimulants, 14.7% were taking tricyclic antidepressants, and 14% were taking serotonin selective reuptake inhibitors. Thus, approximately 30% of the participants were taking an antidepressant. This profile is quite representative of treated narcoleptic patients.[15] By the end of the baseline period, participants experienced little or no change from study entry (Visit 2) in the frequency of narcolepsy symptoms following the discontinuation of prior treatments for narcolepsy (Visit 5).

Intervention Compliance

At least 70% compliance with the interventions was attained by 91.7% of participants during the dose-titration phase (from Visit 5 to Visit 6). During the stable dosing phase (from Visit 6 to visit 7), this level of compliance was achieved for 86.4% of the participants. As expected, the percentage of participants per group that were 70% compliant decreased in inverse proportion to the dose level during the stable dosing phase and ranged from 93.2% for the placebo group to 74.5% for the group taking 9.0 g per day of sodium oxybate; however, the median compliance for each treatment group was at least 100% during both dosing periods.

FOSQ Efficacy Analysis

All sodium-oxybate treatment groups had significant ($p < .001$) within-group changes in the median FOSQ Total score from baseline to Visit 7. As shown in Table 2 and Figure 2, compared with placebo, only the median change in Activity Level and Social Outcome subscales achieved statistical Bonferroni-adjusted significance. When compared with placebo, the group treated with 9.0 g per day of sodium oxybate had statistically significant improvement ($p < .001$) at Visit 7 in all components of the FOSQ except for the Intimacy and Sexual Relationships scale. A dose effect was evident with statistically significant ($p < .01$) changes among doses for the Total score and all FOSQ subscales except for the Intimacy and Sexual Relationships subscale. Effect sizes escalated from small effects for the 6.0-g per day dose of sodium oxybate to large effects for the 9.0-g per day dose.

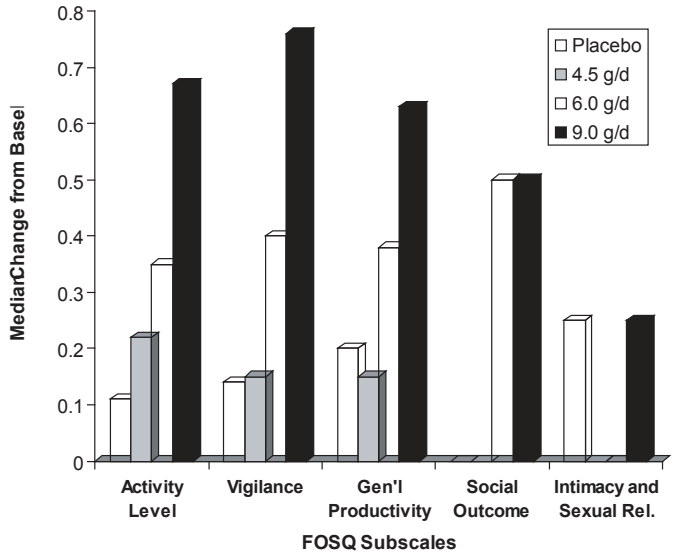

Figure 2—Change in scores from baseline to double-blind endpoint. The mean change from baseline in Functional Outcomes of Sleep Questionnaire (FOSQ) subscale scores following intervention are presented for the placebo and sodium oxybate doses of 4.5, 6.0, and 9.0 g per day.

Safety and Adverse Events

Adverse events (AEs) were experienced by 69% of participants who received double-blind trial medication and three experienced serious adverse events. The nature of the adverse and serious adverse events are described elsewhere.[4,12]

Twenty participants who were treated with sodium oxybate discontinued trial medication as a result of treatment-emergent AEs or serious AEs. Discontinuing treatment appeared to increase with dose level, from 1 of 68 participants at the 4.5-g per day dose to 15 of 55 in the 9.0-g per day dose. The AEs that most commonly led to discontinuing treatment (alone or in combination with other AEs) included nausea (5 participants), dizziness (4 participants), hypoesthesia (3 participants), somnolence (3 participants), chest pain (3 participants), and dyspnea (3 participants).

DISCUSSION

Compared with placebo-treated patients, participants treated with doses of sodium oxybate of 6.0 g per day and 9.0 g per day experienced statistically significant improvements in functional status, a component of quality of life. Sodium oxybate had a positive effect on most components of quality of life, as demonstrated by an increased Total score on the FOSQ, as well as improvements in the Activity Level, Vigilance, General Productivity, and Social Outcomes subscales. A dose response was demonstrated with the greatest effect size obtained on 9.0 g per day. The treatment also appeared to be safe and well tolerated, especially at the lower doses.

The quality of life of patients with narcolepsy is as poor or worse than patients with Parkinson disease, epilepsy, and obstructive sleep apnea.[8,9] They experience more difficulty than the general population with energy level, social activities, and performing tasks and roles due to physical and emotional limitations.[7,9] Despite treatments with stimulants or anticataplexy medication, patients with narcolepsy still report greater functional limitations than do patients with obstructive sleep apnea who are treated with nasal continuous positive airway pressure.[8] This finding by Teixeir and colleagues[8] suggests that current treatment regimens for narcolepsy may inadequately ameliorate the functional difficulties reported by this population.

The improvement in cataplexy and daytime sleepiness that has been previously demonstrated with the administration of sodium oxybate[1,3,4,12] likely results in increased ability to conduct multiple daily activities. Our study is the first to document the positive effect on everyday life when patients with narcolepsy are treated with sodium oxybate. Those domains of quality of life most affected by narcolepsy improved, compared with placebo, with participants receiving active medication reporting greater productivity, activity, vigilance, and social interaction. The magnitude of this change was not only statistically robust, but also clinically important, indicating that incorporating this treatment into the patient's medical management can have a profound affect on quality of life.

The greatest change in functioning was observed in the highest-dose group and a clear dose-response pattern was demonstrated. There was no significant change at 4.5 g per day; however, clinically relevant improvement was noted in 2 of the 5 subscales at the 6.0 g per day dose and more global enhancement at the 9.0 g per day dose, with 4 of the 5 subscales showing improvement. This dose response is similar to that reported for improvements in quality of life of patients with narcolepsy following treatment with modafinil.[9] Patients treated with 400 mg of modafinil had a greater response than those on the 200-mg dose. Although the Beursterien[9] study utilized the SF-36, a generic measure of quality of life, it is interesting that those areas of daily living that were positively affected by modafinil, as measured by this instrument—specifically, social functioning, activity, and general productivity—were also improved by sodium oxybate, as measured with the FOSQ. The subscales reflective of these domains for the FOSQ and the SF-36 are significantly related (r = 0.36, 0.32, 0.36, and 0.36, respectively).[13]

The similarity in results between these two studies utilizing different treatments to address daytime sleepiness may suggest that improvements in narcolepsy symptoms enable the patient to resume those activities previously limited. Moreover, the fact that 50% of the participants on the 9.0 g per day dose were on modafinil during the study and still obtained substantial improvement in daily functioning suggests that sodium oxybate may further enhance functioning in those receiving other treatments for narcolepsy. Thirty-four percent of the participants on the 9.0 g per day dose were also on other centrally acting sympathomimetic medications, with the greatest proportion of participants (16.4%) being on methylphenidate hydrochloride.

There was no statistically reliable change in the Intimate and Sexual Relationships subscale at any dose. As the baseline, scores for this subscale were the highest of any subscale at any dose; this could reflect a ceiling effect. The high score values indicate that this activity is least affected by the impairments imposed by narcolepsy. However, the possibility also exists that individuals were more reluctant to indicate that they had difficulty in this area.

In this study and during a previously published 12-month open-label study,[12] there were minimal adverse events and changes in baseline laboratory values that would indicate clinically significant drug-related concerns. There were few serious AEs, and only one experienced by one participant was considered to be drug related. Thus, it appears that sodium oxybate is generally well tolerated.

CONCLUSION

Sodium oxybate is currently the only medication approved in the United States for the treatment of cataplexy associated with narcolepsy. This controlled clinical trial provides additional data demonstrating improvements in quality of life following the nocturnal administration of sodium oxybate that extend beyond cataplexy and daytime sleepiness. Treatment with sodium oxybate was associated with significant, dose-related improvements in Total FOSQ Scores, as well as in the Activity Level, General Productivity, Vigilance and Social Outcome subscales. This relatively safe medication improves daily functioning, enhancing quality of life. The use of a placebo group and a sample, comprising typical narcolepsy patients who remained on their doses of stimulants, clearly demonstrates this benefit and adds to the robust nature and generalizability of the findings.

ACKNOWLEDGMENT

Analyses of data were independently performed by a contract research organization that certified the study was conducted in compliance with Good Clinical Practice. This study was conducted by the Xyrem® International Study Group.

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