Sodium Oxybate Improves Excessive Daytime Sleepiness in Narcolepsy

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Study Objectives: To assess the effectiveness of sodium oxybate therapy, modafinil therapy and the combination of the two for excessive daytime sleepiness in narcolepsy patients previously taking modafinil.

Design: Double-blind, placebo-controlled, multicenter study.

Setting: Forty-four sites in the United States, Canada, the Czech Republic, France, Germany, the Netherlands, Switzerland, and the United Kingdom.

Participants: Two hundred seventy- adult patients with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of excessive daytime sleepiness.

Interventions: Patients received unchanged doses of modafinil (with sodium-oxybate placebo) during a 2-week baseline phase. Following a baseline polysomnogram and Maintenance of Wakefulness Test, they were randomly assigned to 1 of 4 treatment groups: sodium-oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus sodium-oxybate placebo, or sodium oxybate plus modafinil. Sodium oxybate was administered as 6 g nightly for 4 weeks and was then increased to 9 g nightly for 4 additional weeks. The primary efficacy measure was the Maintenance of Wakefulness Test; secondary measures included the Epworth Sleepiness Scale, diary recordings, and the Clinical Global Impression-change scale.

Results: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the Maintenance of Wakefulness Test decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks ($p < .001$). In the sodium-oxybate group, there was no decrease in sleep latency, suggesting that this drug was as efficacious in treating the excessive daytime sleepiness as the previously administered modafinil. In contrast, the sodium-oxybate/modafinil group demonstrated an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes ($p < .001$), suggesting that this combination of drugs produced an additive effect. The sodium-oxybate group also demonstrated a decrease in median average Epworth Sleepiness Scale scores, from 15 to 12.0, whereas the sodium-oxybate/modafinil group decreased from 15.0 to 11.0 (for both, $p < .001$). The Clinical Global Impression-Change scale demonstrated similar results.

Conclusions: Sodium oxybate and modafinil are both effective for treating excessive daytime sleepiness in narcolepsy, producing additive effects when used together. Sodium oxybate is beneficial as both monotherapy and as adjunctive therapy for the treatment of excessive daytime sleepiness in narcolepsy.

Keywords: Sodium oxybate, narcolepsy, excessive daytime sleepiness, modafinil, polysomnography, gamma-hydroxybutyrate

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INTRODUCTION

NARCOLEPSY IS AN UNCOMMON NEUROLOGIC DISEASE THAT SPECIFICALLY AFFECTS THE GENERATION AND ORGANIZATION OF SLEEP AND WAKEFULNESS.[1] Of the varied symptoms that may comprise the narcolepsy syndrome, excessive daytime sleepiness (EDS) is ubiquitous. Other symptoms may include cataplexy, hypnagogic hallucinations, and sleep paralysis, each believed to represent components of rapid eye movement sleep that abnormally occur during periods of wakefulness. In addition, disrupted nocturnal sleep or sleep fragmentation is considered a symptom of narcolepsy.[1]

Disclosure Statement

This was an industry supported study by Orphan Medical Inc. Dr. Black has received research support from GlaxoSmithKline, Organon, and Cephalon Inc.; and has participated in speaking engagements supported by GlaxoSmithKline and Takeda Pharmaceuticals. Dr. Houghton was an employee for Orphan Medical Inc during the study and in this capacity wrote the protocol that generated the data. All data entry and analysis was conducted by external contract services, and has been submitted to the FDA for independent analysis.

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Until recently, drug therapy for EDS has consisted primarily of amphetamines and related stimulants, including methylphenidate and dextroamphetamine, that increase alertness and improve daytime performance.[2] It has been reported that these medications may only improve alertness levels to about 70% of normal individuals,[3] and adverse events commonly include headaches, nervousness, irritability, tremor, insomnia, anorexia, and palpitations. Tolerance to the alerting effect of these drugs develops in as many as 30% of patients using these medications.[4]

Currently, a standard of care for the treatment of EDS in narcolepsy is modafinil.[2] Chemically distinct and to some extent pharmacologically unrelated to other stimulants, modafinil has an improved safety profile and lower abuse potential, as compared with older stimulants; however, it may not be as potent and its use usually does not reduce EDS to normal levels.[5] In addition, modafinil provides no benefit for cataplexy or disrupted nighttime sleep, necessitating the use of other drugs for these symptoms in some patients.

Short- and long-term studies[6,7] and a long-term safety study[8] with sodium oxybate led to its approval by the U.S. Food and Drug Administration for the treatment of cataplexy (Xyrem®, Orphan Medical, Inc.); however, alternative therapy has been used to treat EDS. Although the use of sodium oxybate has some advantages over the previously used agents for the treatment of cataplexy, a single therapeutic agent that also provides significant benefits for the treatment of EDS and fragmented nighttime sleep without the

development of tolerance or intolerable adverse events would represent a significant advancement for the treatment of narcolepsy.

Independent investigations with sodium oxybate, the sodium salt of γ-hydroxybutyrate, for the treatment of narcolepsy have demonstrated that this drug can markedly improve narcolepsy symptoms, including the quality of nocturnal sleep and subjective improvements in EDS.[6,9-11] The results of a pilot study that used objective measures provided data demonstrating that the beneficial effects of sodium oxybate for the treatment of narcolepsy extend to improvements in fragmented nighttime sleep and EDS.[12] These results have recently been confirmed in a much larger follow-up study, indicating that nightly administration of sodium oxybate produces dose-related increases i slow-wave sleep and delta power that coincided with significant improvements in subjective and objective measures of EDS symptoms.[13]

In all of the above studies, the improvements produced by sodium oxybate occurred while the majority of patients (approximately 80%) remained on stimulant medications; that is, for most patients, these improvements were incremental to those already achieved by the use of stimulant drugs. The following double-blind, placebo-controlled trial represents the first trial that attempted to characterize the efficacy of sodium oxybate as a single agent, or in combination with modafinil, for the treatment of EDS in a large population of patients with narcolepsy.

METHODS

Subjects

Unlike previous sodium-oxybate trials, this study did not include the presence of cataplexy as an enrollment criterion. Patients were included in the trial if they were 18 years of age or older and met the following criteria: (1) fulfilled the International Classification of Sleep Disorders criteria for the diagnosis of narcolepsy; (2) were taking a stimulant medication for the treatment of EDS for at least 3 months and were taking stable doses of modafinil (200 to 600 mg/day) for at least 1 month immediately prior to the trial or were taking stable doses of modafinil for at least 6 weeks prior to trial entry; (3) were willing to forego operating a motor vehicle or heavy machinery for the duration of the trial, if indicated; and (4) expressed a willingness to complete the study protocol and signed an informed consent.

The following criteria were used to exclude patients from the trial: (1) the use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment; (2) sleep apnea disorder, defined as an Apnea Index > 10 per hour or an Apnea Hypopnea Index > 15 per hour, or any other cause of daytime sleepiness, such as periodic limb movements of sleep; (3) concurrent use of hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants or clonidine; (4) a current or recent history of a substance abuse disorder; (5) a serum creatinine greater than 2.0 mg/dL, alanine aminotransferase or aspartate aminotransferase more than twice the upper limit of normal, or bilirubin more than 1.5 times the upper limit of normal; (6) a clinically significant dysrhythmia or a history of myocardial infarction within the prior 6 months; (7) history of seizure disorder, clinically significant head trauma, or past invasive intracranial surgery or; (8) an occupation requiring variable shift work or routine night shifts.

Trial Medications

Trial medications included a liquid solution containing sodium oxybate at a concentration of 500 mg/mL (Xyrem®, Orphan Medical, Inc., Minnetonka, MN); sodium-oxybate placebo consisted of a solution of sodium citrate that was equimolar with respect to sodium. The placebo solution has previously been shown to be indistinguishable from sodium-oxybate solution (Orphan Medical, Inc., data on file). Modafinil tablets, 200 mg, (Provigil®, Cephalon Inc., West Chester, PA) were enclosed in lactose-filled gelatin capsules, and the modafinil placebo consisted of identical capsules containing lactose only. Prior testing demonstrated that modafinil tablet encapsulation did not alter the dissolution characteristics of the drug. In this study, patients were permitted to remain on antidepressant medications at unchanged doses throughout the trial.

Patients were cautioned about the use of alcoholic beverages at any time during the trial. In addition, patients were cautioned about the use of potentially sedating medications, such as analgesics or muscle relaxants and were encouraged to discuss the use of over-the-counter and prescription medicines with the investigator.

Study Design

Patients were evaluated for trial inclusion at Visit 1 (see Figure 1). During this visit, inclusion and exclusion criteria were reviewed; medical history, physical examination and vital sign information was recorded; and samples for clinical laboratory testing were obtained. After providing informed consent, enrolled patients began training in keeping a daily diary.

Clinic Visit 2 occurred 1 to 2 weeks later when an overnight polysomnogram (PSG) was performed followed by a Maintenance of Wakefulness Test (MWT) while patients remained on established doses of modafinil and any other concomitant medications to assess the baseline efficacy of modafinil for the treatment of EDS. PSGs were scored the following day to identify comorbid conditions that could cause daytime sleepiness, such as obstructive sleep apnea or periodic limb movements of sleep. Patients meeting inclusion criteria entered the 2-week single-blind baseline period and initiated single-blind modafinil at their customary doses of 200 to 600 mg per day and nightly placebo sodium-oxybate solution. Patients were instructed to take placebo sodium oxybate in equally divided doses at bedtime and repeated 2.5 to 4 hours later.

Visit 3 included baseline PSG and MWT recordings for all patients before beginning the treatment phase, according to prior double-blind randomization: Group 1: placebo sodium oxybate + placebo modafinil (placebo group), Group 2: sodium oxybate + placebo modafinil (sodium-oxybate group), Group 3: placebo sodium oxybate + modafinil (modafinil group), and Group 4: sodium oxybate + modafinil (sodium-oxybate/modafinil group)

The patients who were randomly assigned to Groups 3 and 4 continued to receive their customary doses of modafinil in blinded fashion. Patients randomly assigned to Groups 2 and 4 received sodium oxybate at a dose of 6 g nightly, administered in 2 equally divided doses at bedtime and again 2.5 to 4 hours later for the initial 4-week period of the study. Patients in Groups 1 and 3 received an equivalent volume of placebo sodium-oxybate solution.

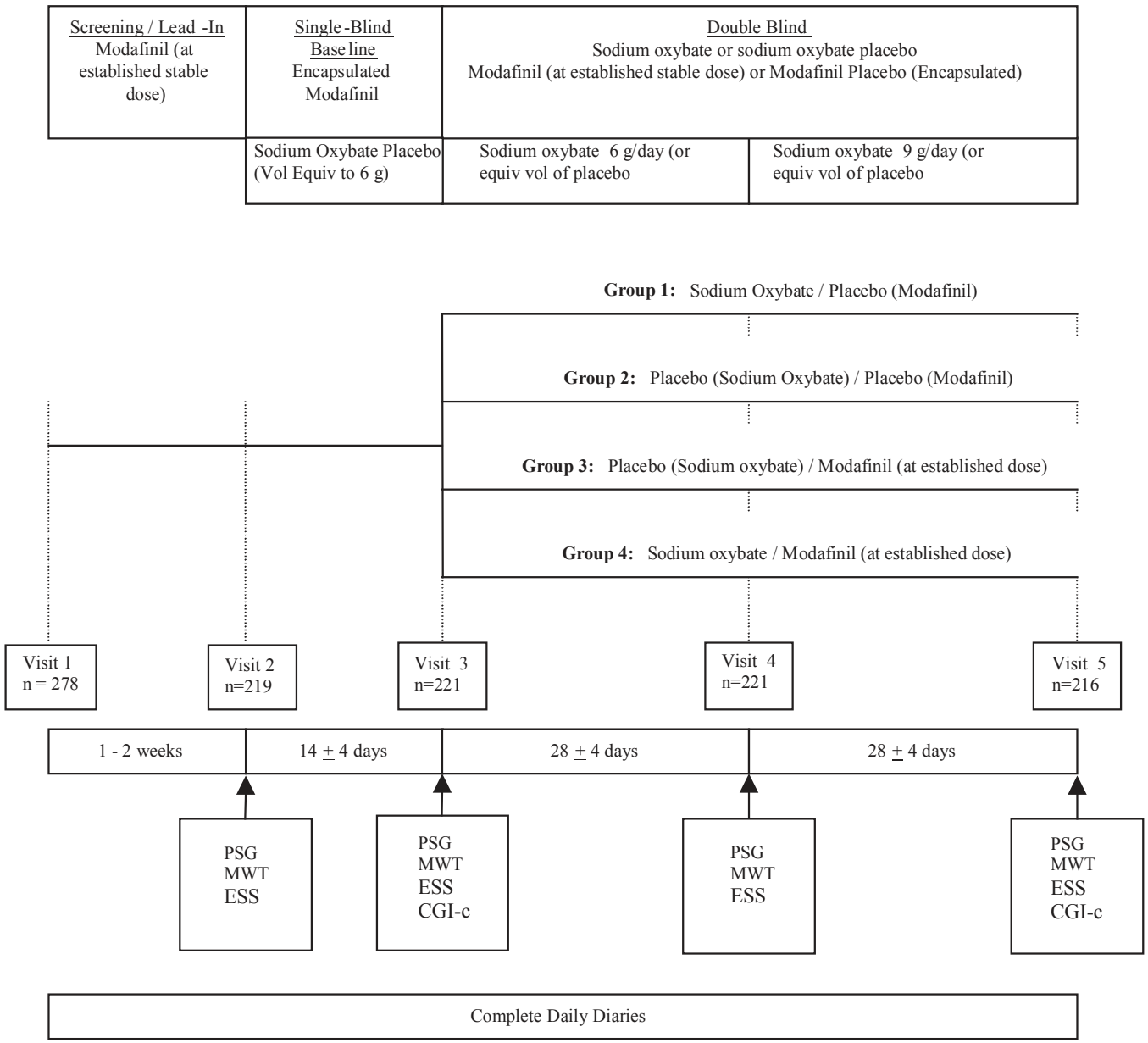

Figure 1—Study Design. At Visit 1, patients were evaluated for inclusion into the trial. After a period of 1 to 2 weeks, to allow for review of hematology and blood chemistry results as well as diary training, patients returned to the clinic for Visit 2. While on stable doses of modafinil, patients underwent a polysomnogram (PSG) and Maintenance of Wakefulness Test (MWT). The overnight PSG was scored the next day to ensure that the patients did not have other conditions that could be primary causes of daytime sleepiness, such as obstructive sleep apnea or periodic limb movements of sleep. After Visit 2, all patients entered a 2-week baseline phase, remaining on modafinil in single-blind fashion while receiving sodium oxybate placebo. At Visit 3, patients were randomly assigned to 1 of 4 treatment groups, as shown. After 4 weeks, the dose of sodium oxybate (or placebo equivalent) was increased from 6 g nightly to 9 g nightly for the remainder of the trial. The measures of efficacy and safety were performed during the trial, as indicated. The number of patients shown at each visit represents the number providing MWT data. ESS refers to Epworth Sleepiness Scale; CGI-c, the Clinical Global Impression-change score.

Patients returned to the clinic for Visit 4, four weeks later when efficacy and safety assessments were performed, including PSG and MWT measures. Patients continued taking modafinil or placebo modafinil at their prescribed dose; however, the dose of sodium oxybate was increased to 9 g nightly in 2 equally divided doses. Patients assigned to placebo sodium oxybate increased their dose of placebo solution by an equiva lent volume. All patients continued taking their assigned drug regimen for an additional 4 weeks before returning to the clinic for final efficacy and safety assessments at Visit 5.

Study Endpoints

The primary measure of efficacy in this trial was the 20-minute MWT, which was performed following a nocturnal overnight PSG at Visits 2, 3, 4, and 5 according to validated standards.[14] Briefly, the MWT began at approximately 10:00 AM and consisted of four 20-minute tests, 2 hours apart. Patients were required to recline in a quiet, dimly lit bedroom and instructed to remain awake for as long as possible. The trial was concluded after the onset of sleep or after 20 minutes if sleep did not occur. The onset of sleep was recorded using a standard PSG montage and defined as 3 consecutive 30-second epochs of stage 1 sleep or 30 seconds of sleep

stage 2, 3, 4, or rapid eye movement sleep. Secondary measures of efficacy included the Epworth Sleepiness Scale (ESS)[15] performed at Visits 2 through 5 and the Clinical Global Impression of Severity and the Clinical Global Impression of Change (CGI-s and CGI-c), which were performed at Visits 3 and 5, respectively. Daily diaries containing patient reports of inadvertent naps or sleep attacks, subjective changes in sleep quality, and adverse drug events (AE) were reviewed at each clinic visit.

Safety Measures

Safety assessments made at Visits 1 and 5 included a physical examination and measurement of vital signs. Clinical laboratory tests were performed at a central laboratory and included hematology (hemoglobin, hematocrit, red blood cells, white blood cells, and differential count), clinical chemistry (blood urea nitrogen, glucose, creatinine, total protein, albumin, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and total bilirubin), and a serum pregnancy test, if applicable. Clinically significant laboratory parameters that were outside the reference range of the central laboratory were repeated. In addition, a 12-lead electrocardiogram was performed at Visit 1 and repeated at Visit 5, if considered to be clinically indicated by the study investigator.

All AEs reported during the trial were followed until resolution of the event. In each instance, the signs and symptoms associated with the event; duration, severity, relationship to treatment or other therapy; any remedial action; and the outcome of each event were recorded. All patients who received trial medication during the double-blind phase but later chose to discontinue the trial for any reason prior to completion were asked to provide a final measurement of vital signs and clinical laboratory tests before discontinuation. If the early termination was due to an AE, the patient was followed until satisfactory resolution or determination of outcome of the event was obtained.

Statistics

The primary endpoint analysis was conducted on the intent-to-treat (ITT) population. The primary analysis was an ITT analysis at Visit 5. If data were unavailable for a patient, the last observation carried forward technique was used with the last postbaseline observation available for that patient. MWT data were analyzed using analysis of covariance (ANCOVA) and CGI-c data were analyzed using nonparametric ANCOVA. Due to nonnormal data distribution, ESS scores and average weekly inadvertent naps or sleep attacks were evaluated using nonparametric ANCOVA based on the rank-transformation of baseline and endpoint. Two-sided p values were reported, and the level of significance was tested at .05.

In the analysis of safety data, AEs were summarized by treatment group, and their incidence was compared using Fisher exact test. For laboratory data, the mean changes from baseline were compared across treatment groups using analysis of variance. The significance of changes from baseline in laboratory parameters within each treatment group was evaluated with paired t tests.

Ethics

The study was conducted at 44 sites in the United States, Canada, the Czech Republic, France, Germany, Netherlands, Switzerland, and the United Kingdom. The protocol used in this study was approved by the Institutional Review Board or Ethics Board of each participating trial center. 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.

Table 1—Patient Demographics by Treatment Group[a]

	Placebo n = 55	Sodium oxybate n = 50	Modafinil n = 63	Sodium oxybate/ modafinil n = 54	Total N = 222
Sex, no. (%)					
Men	24 (43.6)	26 (52.0)	32 (50.8)	25 (46.3)	107 (48.2)
Women	31 (56.4)	24 (48.0)	31 (49.2)	29 (53.7)	115 (51.8)
Race, no. (%)					
White	43 (78.2)	47 (94.0)	57 (90.5)	48 (88.9)	195 (87.8)
Black[b]	11 (20.0)	2 (4.0)	5 (7.9)	5 (5.6)	21 (9.5)
Asian	0	1 (2.0)	0	0	1 (0.5)
Other	1 (1.8)	0	1 (1.6)	3 (5.6)	5 (2.3)
Mean age ± SD, y	41.0 ± 13.4	35.1 ± 12.9	38.9 ± 15.6	38.9 ± 15.9	38.6 ± 14.6
Mean weight ± SD, kg	84.7 ± 19.9	81.8 ± 17.9	80.6 ± 15.1	79.4 ± 16.9	81.6 ± 17.4

[a]Intention-to-treat group.
[b]There were significantly more black patients in the placebo group compared with other treatment groups ($p < .05$)

RESULTS

A total of 278 patients were enrolled in the study, of which 231 were randomly assigned to 1 of the 4 treatment groups. The ITT population consisted of 222 patients who received at least 1 dose of double-blind medication and provided baseline data at Visit 3 and efficacy data at Visit 4, Visit 5, or both Visits 4 and 5. Patient demographics of the ITT population are provided in Table 1.

Excessive Daytime Sleepiness

The MWT

Compared with the placebo group, the other 3 treatment groups maintained significantly longer mean average daytime sleep latencies after 8 weeks of treatment, as determined by MWT recordings. In the placebo group, the mean average sleep latency was 6.87 minutes after 8 weeks, compared with 11.97 minutes for the sodium-oxybate group ($p < .001$) and 13.15 minutes for the sodium-oxybate/modafinil group ($p < .001$). The modafinil group displayed a mean average sleep latency of 9.86 minutes, which also remained significant compared with the placebo group ($p = .006$) (Table 2). As shown in Figure 2, the greatest amount of change occurred during the initial 4 weeks of the trial.

From the beginning of the baseline period to the end of double-blind treatment period, the placebo group demonstrated a significant within-group decrease in daytime sleep latency of 2.72 minutes ($p < .001$). This occurred as a consequence of withdrawal from modafinil, demonstrating the efficacy of modafinil for the treatment of EDS. In contrast, neither the sodium-oxybate nor modafinil groups demonstrated within-group changes in sleep latency at the end of the trial, i.e., there were no significant dif-

Table 2—Maintenance of Wakefulness Test[a]

	Placebo n = 55	Sodium oxybate n = 50	Modafinil n = 63	Sodium oxybate/ modafinil n = 54
Visit 3	9.74 ± 6.57	11.29 ± 6.40	10.48 ± 6.03	10.43 ± 6.77
	n = 55	n = 49	n = 63	n = 54
Visit 5	6.87 ± 6.14	11.97 ± 7.21	9.86 ± 5.89	13.15 ± 6.91
	n = 53	n = 48	n = 62	n = 53
Change[b]	-2.72 ± 4.54	0.58 ± 5.68	-0.53 ± 4.36	2.68 ± 5.07
Significance[c]	—	p < .001	p = .006	p < .001

[a]Data are presented as the mean average of 4 trials per patient ± SD, in minutes, last observation carried forward. Visit 3 followed 2 weeks of single-blind modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses.
[b]Change from Visit 3 to Visit 5.
[c]Compared with placebo.

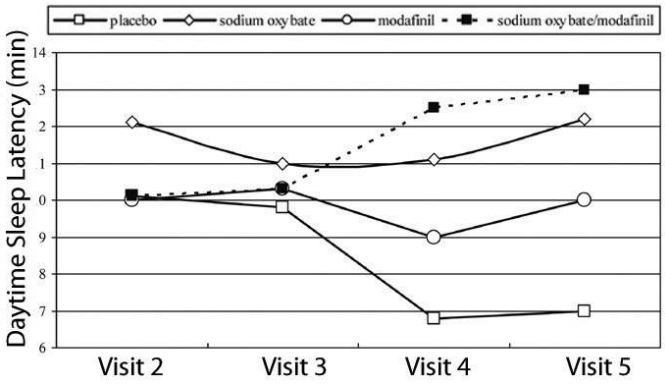

Figure 2—Maintenance of Wakefulness Test. At Visit 3, patients were randomly assigned to receive placebo treatment, modafinil only, sodium oxybate 6 g nightly only, or sodium oxybate 6 g nightly plus modafinil. At Visit 4, the sodium-oxybate dose was increased to 9 g nightly. At Visit 5, the placebo group demonstrated a decrease in mean average daytime sleep latency from 9.74 to 6.87 minutes ($p < .001$ compared with baseline) following withdrawal from modafinil treatment, whereas the sodium-oxybate and modafinil groups experienced no change. The mean average sleep latency in patients receiving the sodium-oxybate/modafinil combination increased from 10.43 minutes to 12.91 minutes on the Maintenance of Wakefulness Test (MWT) ($p < .001$ compared with placebo).

ferences between the sodium-oxybate and modafinil treatment groups. The mean average sleep latency for both groups was significantly longer than that of placebo-treated patients at the end of the trial.

The sodium-oxybate/modafinil group demonstrated a mean average sleep latency increase of 2.68 minutes ($p < .001$), compared with baseline, representing the incremental improvement in EDS produced by the addition of sodium oxybate over the response produced by modafinil alone.

ESS Scores

The sodium-oxybate and sodium-oxybate/modafinil groups demonstrated significant reductions in ESS scores, compared with patients treated with placebo at the end of the trial (for each, $p < .001$) whereas the scores for the modafinil-treated patients did not significantly change, as expected, and were not different from the placebo group (Table 3).

Table 3—Epworth Sleepiness Scale Scores[a]

	Placebo n = 55	Sodium oxybate n = 50	Modafinil n = 63	Sodium oxybate/ modafinil n = 54
Visit 3	16.0	15.0	14.0	15.0
	n = 54	n = 48	n = 61	n = 54
Visit 4	17.0	13.0	15.0	11.5
	n = 53	n = 48	n = 62	n = 50
Significance	—	p < .001	p = .071	p < .001
Visit 5	16.0	12.0	15.0	11.0
	n = 53	n = 49	n = 63	n = 53
Significance	—	p < .001	p = .767	p < .001

[a]Data are presented as median average, in minutes, last observation carried forward. Visit 3 followed 2 weeks of single-blind modafinil at previously established doses. Visit 4 followed 4 weeks of placebo or sodium oxybate 6 g nightly and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses. Significance was as compared with placebo.

In the sodium-oxybate group, following the discontinuation of modafinil, the ESS scores decreased from a median average of 15 to 12 by the end of the 8-week double-blind treatment phase and, similarly, from 15 to 11 in the sodium-oxybate/modafinil group (for each, $p < .001$ compared with baseline). In contrast, the placebo group demonstrated no change in ESS scores during the same period.

Weekly Inadvertent Naps or Sleep Attacks

The patients in the sodium-oxybate and sodium-oxybate/modafinil groups had significantly fewer weekly sleep attacks at the end of the trial, as compared with modafinil and placebo groups. In the sodium-oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks ($p < .001$) and the sodium-oxybate/modafinil group demonstrated a decrease from 11.82 to 5.55 ($p < .001$). There was no significant difference between the modafinil- and placebo-treated groups (Table 4).

Compared with baseline, the median within-group reductions in the number of weekly sleep attacks was significant for patients treated with sodium oxybate alone (-2.04; $p = .005$) and the sodium-oxybate/modafinil combination group (-2.85; $p < 0.001$). The patients in the placebo-treated and modafinil-treated groups remained essentially unchanged during the same period.

CGI-s and CGI-c Assessments

For each patient, the overall severity of narcolepsy symptoms was assessed by a trial investigator using the CGI-s assessment at Visit 3, prior to the blinded treatment phase, while all patients remained on stable modafinil treatment. The baseline CGI-s assessment indicated that the patients enrolled in the study were considered to be markedly ill despite treatment with modafinil. At the conclusion of the trial, the sodium-oxybate group and sodium-oxybate/modafinil group each demonstrated overall improvements in their clinical condition, compared with the placebo group ($p = .002$ and $p = .023$, respectively). In contrast, the pla-

Table 4—Inadvertant Naps/Sleep Attacks[a]

	Placebo n = 55	Sodium oxybate n = 50	Modafinil n = 63	Sodium oxybate/ modafinil n = 54
Visit 3	15.23 ± 19.7	10.05 ± 12.9	12.41 ± 12.8	11.82 ± 11.3
	n = 55	n = 50	n = 60	n = 54
Visit 4	17.55 ± 18.0	12.24 ± 30.1	13.72 ± 18.6	7.19 ± 6.4
	n = 53	n = 48	n = 62	n = 52
Significance	—	p = .005	p = .006	p < .001
Visit 5	19.75 ± 32.6	7.10 ± 9.1	12.5 ± 18.5	5.55 ± 5.9
	n = 55	n = 50	n = 62	n = 54
Significance	—	p < .001	p = .073	p < .001

[a]Data are presented as the mean ± SD for the 2 weeks preceding each visit, missing data excluded. Visit 3 followed 2 weeks of single-blind modafinil at previously established doses. Visit 4 followed 4 weeks of placebo or sodium oxybate 6 g nightly and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses. Significance was as compared with placebo.

cebo and the modafinil groups were judged as demonstrating no significant change in disease severity (Figure 3).

Based on the CGI of the investigators, a significantly higher percentage of patients in the sodium-oxybate and sodium-oxybate/modafinil groups had a successful treatment response. Compared with the placebo group, 48.0% (p = .002) in the sodium-oxybate group and 46.3% (p = .023) of the sodium-oxybate/modafinil group were judged to be Much Improved or Very Much Improved, compared with 21.8% in the placebo group and 19% in the modafinil group.

Safety

At least 1 AE was reported in 151 of 231 treated patients (65.4%) who entered the double-blind treatment phase of the study. Compared with the incidence of AEs reported in the sodium-oxybate (60%), modafinil (54.0%), or placebo groups (69.6%), a somewhat greater number of AEs were reported in the sodium-oxybate/modafinil group (78.9%). Among all patients, the most common treatment-emergent AEs included headache (15.2%), nausea (11.7%), dizziness (9.1%), nasopharyngitis (6.1%), vomiting (6.1%), and somnolence (5.6%). Of these, only nausea, vomiting, and dizziness were statistically significant different between treatment groups. The AEs occurring in all patients with a frequency of 5% or greater are provided in Table 5.

Nausea and vomiting occurred with highest frequency in the sodium-oxybate groups, whereas the incidence of dizziness was highest in the sodium-oxybate/modafinil group. Statistically significant differences between treatment groups were also noted with respect to tremor (4.8%) and paresthesia (2.6%), occurring only in patients receiving sodium oxybate or sodium oxybate plus modafinil, and upper respiratory tract infections (2.2%), occurring primarily in the placebo group.

The number of patients who withdrew from the study early as the result of a treatment-emergent AE or serious AE was greatest in the sodium-oxybate/modafinil group (6), compared with the sodium oxybate (4), modafinil (2) or placebo groups (1). Serious AEs reported in 4 patients included (MedDRA coding terminology): pregnancy (protocol violation), abdominal pain, palpitations,

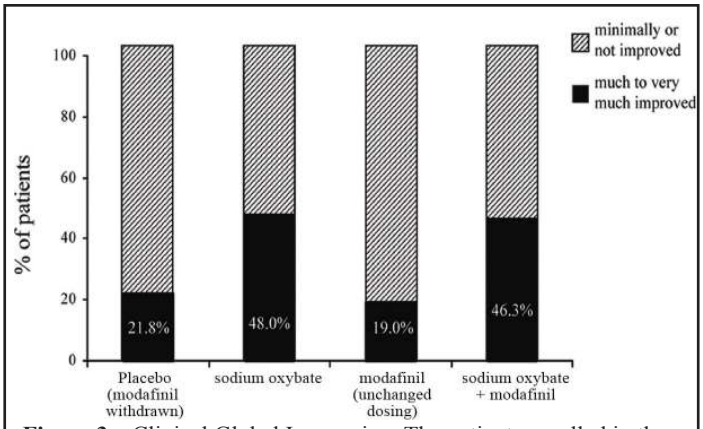

Figure 3—Clinical Global Impression. The patients enrolled in the study were considered to be markedly ill at Visit 3. At the conclusion of the trial, treatment with sodium oxybate, alone and together with modafinil, resulted in significant overall improvements in the clinical condition of these patients, as compared with the placebo-treated patients (p = .002 and p = .023, respectively). In contrast, the placebo- and the modafinil-treated patients demonstrated no significant change in symptoms. CGI-c refers to the Clinical Global Impression-change score.

and a psychotic disorder due to a general medical condition (narcissistic personality disorder); however, the only event deemed drug-related was the psychotic disorder, which occurred in the sodium-oxybate/modafinil group.

Nine patients in the 3 active drug groups experienced 13 treatment-emergent AEs involving laboratory parameters that were considered to be mild or moderate in severity. Group mean changes from baseline in several laboratory parameters and vital signs were statistically significant but were not considered to be clinically important. Potentially treatment-related AEs included increased serum aspartate aminotransferase and alkaline phosphatase in 1 patient and increased lactate dehydrogenase level in 1 patient, both in the modafinil-only group, and increased serum glucose concentration in 1 patient in the sodium-oxybate/modafinil group.

Four patients in the sodium-oxybate/modafinil treatment group experienced potentially treatment-related changes in vital signs. These AEs included hypertension, hypotension, hyperventilation, and low-grade fever. Each was mild or moderate in severity and occurred in 1 patient.

DISCUSSION

In this trial, the beneficial effects of nocturnal sodium-oxybate administration to patients with narcolepsy was demonstrated using both objective and subjective measures of EDS, including MWT, ESS, and the number of weekly sleep attacks. In addition, the clinical trial investigators judged a significant number of patients treated with sodium oxybate to be much improved or very much improved with respect to their overall disease state. As determined by MWT measures, sodium oxybate alone was as effective as modafinil for the treatment of EDS and significantly more efficacious, as measured by ESS and the number of weekly inadvertent naps or sleep attacks, as well as more efficacious than modafinil in CGI.

As has been shown in previous sodium-oxybate studies,[6,8,12] the improvements in EDS, as measured by MWT and the number of weekly sleep attacks, were additive with concurrently

Table 5—Treatment-Emergent Adverse Events Experienced by at Least 5% of all Patients

System Organ Class Preferred Term	Placebo n = 56	Sodium oxybate n = 55	Modafinil n = 63	Sodium oxybate+ modafinil n = 57	Total n = 231	p-value
Any Adverse Event	39 (69.6)	33 (60.0)	34 (54.0)	45 (78.9)	151 (65.4)	0.023
Gastrointestinal						
Nausea	1 (1.8)	12 (21.8)	2 (3.2)	12 (21.1)	27 (11.7)	< 0.001
Vomiting	0	7 (12.7)	2 (3.2)	5 (8.8)	14 (6.1)	0.013
Diarrhea	0	2 (3.6)	2 (3.2)	3 (5.3)	7 (3.0)	0.440
Dry mouth	1 (1.8)	0	1 (1.6)	3 (5.3)	5 (2.2)	0.336
Infection						
Nasopharyngitis	4 (7.1)	5 (9.1)	3 (4.8)	2 (3.5)	14 (6.1)	0.611
Upper respiratory tract	4 (7.1)	1 (1.8)	0	0	5 (2.2)	0.015
Musculoskeletal						
Arthralgia Nervous	1 (1.8)	4 (7.3)	3 (4.8)	0	8 (3.5)	0.142
Headache	12 (21.4)	5 (9.1)	7 (11.1)	11 (19.3)	35 (15.2)	0.185
Dizziness	3 (5.4)	4 (7.3)	2 (3.2)	12 (21.1)	21 (9.1)	0.007
Somnolence	4 (7.1)	4 (7.3)	2 (3.2)	3 (5.3)	12 (5.6)	0.726
Tremor	0	3 (5.5)	0	8 (14.0)	11 (4.8)	<0.001
Paresthesia	0	4 (7.3)	0	2 (3.5)	6 (2.6)	0.022
Psychiatric						
Anxiety	2 (3.6)	0	1 (1.6)	4 (7.0)	7 (3.0)	0.147

Data are expressed as number (%). Adverse events were coded using MeDRA Coding Terminology

administered stimulants. Similarly, the current MWT results demonstrate that the coadministration of sodium oxybate with modafinil provides greater beneficial effects on EDS than the administration of either medication alone. These findings support previous observations that have indicated that the unique pharmacologic properties of sodium oxybate offer an important alternative for the treatment of EDS therapy in narcolepsy.

As expected, patients who were removed from modafinil and received placebo also demonstrated a modest increase in ESS scores; however, the patients who received sodium oxybate, alone and in combination with modafinil, each experienced equally significant improvements in ESS scores, as compared with patients receiving placebo and the patients receiving modafinil alone. These observations suggest that, in this study population, the nocturnal administration of sodium oxybate provides additional subjective benefits that extend beyond those provided by the daytime administration of stimulant medications, such as modafinil. Based on the results of previous studies, this may involve the consolidation of fragmented sleep and significant increases in the duration of slow-wave sleep.[12] Although the MWT indicated an additive beneficial effect when sodium oxybate and modafinil were used together, no additive effects were evident in the ESS.

The CGI-c results also demonstrate that significant overall improvements in the narcolepsy disease state were achieved when patients were treated with sodium oxybate, either alone or in combination with modafinil, as compared with placebo-treated patients, whereas the results in patients treated with modafinil alone were similar to those of placebo-treated subjects. In addition to reductions in EDS, these improvements may also be related to beneficial changes in nocturnal sleep.

The AEs reported by the patients enrolled in the current study were generally mild and consistent with the known AE profiles of sodium oxybate and modafinil. As might be expected, the incidence of AEs occurred with greater frequency in patients randomly assigned to receive the sodium-oxybate/modafinil combination, compared with either medication alone.

Limitations to the trial include a population of study subjects who were already being treated for EDS with modafinil for 3 months or longer prior to trial entry. Thus, AEs due to modafinil may have been underrepresented in these patients because only patients who were able to tolerate the medication entered the trial. That is, patients with problematic side effects caused by modafinil would have discontinued modafinil treatment prior to enrolling into the study. In addition, it remains unknown whether the patients in this study were partial responders or nonresponders to the wake-promoting effect of modafinil prior to their entry into the trial.

CONCLUSION

Sodium oxybate and modafinil are both effective for the treatment of EDS in patients with narcolepsy. The results of the MWT indicated that, when used together, these drugs are more efficacious than either agent alone. The coadministration of sodium oxybate and modafinil is generally well tolerated, although the combination may be associated with a greater incidence of AEs. Currently, sodium oxybate appears to be the only available medication that effectively treats cataplexy, sleep fragmentation, and EDS in patients with narcolepsy.

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