Exploring the relationships of gamma-hydroxybutyrate and sleep on metabolism, physiology, and behavior in humans

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CHAPTER 4

The Nightly Administration of Sodium Oxybate Results in Significant Reduction in the Nocturnal Sleep Disruption of Patients with Narcolepsy

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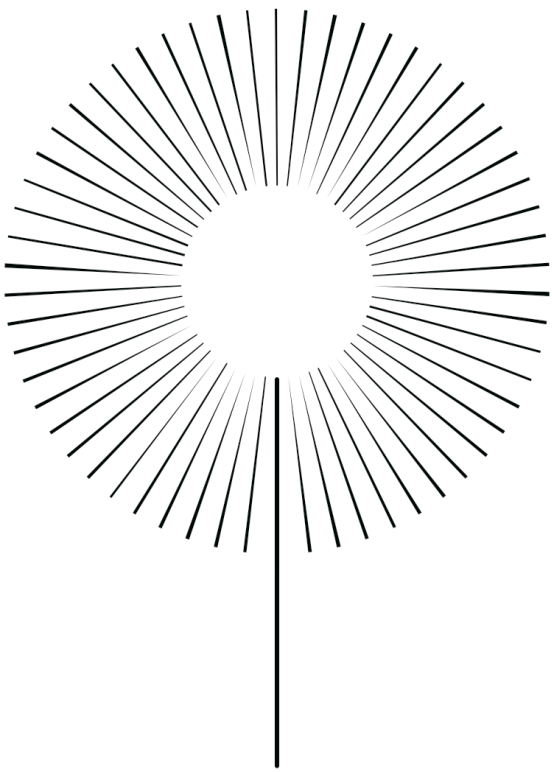

Abstract

Background	Previous studies indicate that nightly sodium oxybate administration reduces nocturnal sleep disruption in narcolepsy. The present study provided an opportunity to further characterize these sleep-related effects in patients with narcolepsy during treatment with sodium oxybate as monotherapy or in combination with modafinil.
Methods	This double-blind, placebo-controlled study enrolled 278 patients with narcolepsy taking modafinil 200–600 mg daily for the treatment of excessive daytime sleepiness (EDS). Following a baseline polysomnogram (PSG) and Maintenance of Wakefulness Test (MWT), patients were randomized to receive treatment with: (1) placebo, (2) sodium oxybate, (3) modafinil, or (4) sodium oxybate + modafinil. PSGs and MWTs were repeated after 4 and 8 weeks. Other efficacy measures included Epworth Sleepiness Scale scores and daily diary recordings.
Results	After 8 weeks, significant changes in sleep architecture among patients receiving sodium oxybate and sodium oxybate/modafinil included a median increase in Stage 3 and 4 sleep (43.5 and 24.25 min, respectively) and delta power and a median decrease in nocturnal awakenings (6.0 and 9.5, respectively). No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone.
Conclusion	In addition to its established efficacy for the treatment of cataplexy and EDS, nightly sodium oxybate administration significantly reduces measures of sleep disruption and significantly increases slow-wave sleep in patients with narcolepsy.

Introduction

Early descriptions of narcolepsy included symptoms of excessive daytime sleepiness (EDS) and attacks of muscle weakness. The symptom subset was later expanded to include the so-called "tetrad" of symptoms, consisting of EDS, cataplexy, hypnagogic hallucination, and sleep paralysis [1,2]. Disrupted nocturnal sleep has long been recognized as a common clinical finding in these patients [3] and was formally added to the clinical description of narcolepsy in 1975 [4].

Investigations using nocturnal polysomnography (PSG) have consistently demonstrated pathological changes in the nocturnal sleep of patients with narcolepsy, including sleep-onset REM periods, increased Stage 1 sleep, diminished Stage 3 and 4 (slow wave) sleep, numerous and sometimes prolonged awakenings after sleep onset, and frequent stage shifts [3,5-8]. Fragmented sleep patterns are also observed in canine [9,10] and rodent [11,12,13] models of narcolepsy.

Therapies for disrupted nocturnal sleep in narcolepsy have consisted primarily of short-acting benzodiazepines[14] and sedating antidepressants [15]. These provide limited benefit and do not improve the daytime symptoms of the disease. Further, traditional pharmacotherapy for the daytime symptoms of narcolepsy has provided little benefit for disrupted nocturnal sleep [16].

In contrast, several investigators over many years have observed that the nightly administration of sodium oxybate improves subjective and objective measures of nocturnal sleep, as well as daytime symptoms, in patients with narcolepsy [6,17-21]. These observations led to larger controlled evaluations of sodium oxybate for the treatment of nocturnal sleep disruption, in addition to cataplexy and EDS, in patients with narcolepsy [22-26].

One of these studies demonstrated that 8 weeks of nightly sodium oxybate administration resulted in robust increases in Stage 3 and 4 sleep and delta power, while the frequency of nocturnal awakenings significantly decreased [26]. These changes in nocturnal sleep quality were associated with significant decreases in the severity and frequency of cataplexy and EDS [25,26].

While the primary efficacy measure in the present study was the change in EDS as measured by the Maintenance of Wakefulness Test (MWT), this study permitted further characterization of the effects of nightly sodium oxybate administration on PSG parameters over an 8-week period. The beneficial effect of sodium oxybate administration on EDS in these patients has been published elsewhere [27].

Methods

Subjects

Enrollment criteria included age 18 years or older, current diagnosis of narcolepsy [28], stable therapy with modafinil (200–600 mg/day) for the treatment

of EDS for ≥1 month prior to the trial, willingness to forego driving or other hazardous activities if recommended by the investigator, and willingness to complete the study by signing an informed consent. Female patients were enrolled if they were surgically sterile, two years post-menopausal, or agreed to use a medically accepted method of birth control during the trial.

Specific exclusion criteria included the use of sodium oxybate or an investigational therapy ≤30 days prior to the trial; diagnosis of sleep apnea disorder or any other cause of daytime sleepiness; a physical or psychiatric illness that placed patients at risk or compromised the objectives of the trial; a history of a substance abuse disorder; serum creatinine >2.0 mg/dL, AST or ALT >2 times the upper limit of normal, or bilirubin >1.5 times the upper limit of normal; a seizure disorder, head trauma, or past invasive intracranial surgery; or an occupation requiring rotating shifts or routine night shifts.

Trial medications

Trial medications included a concentrated solution of sodium oxybate 500 mg/mL (Xyrem®, Jazz Pharmaceuticals, Inc., Palo Alto, CA); sodium oxybate placebo consisted of a sodium citrate solution that was equimolar to sodium oxybate with respect to sodium. 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 (Jazz Pharmaceuticals, Inc., data on file). Patients were cautioned about the use of potentially sedating medications, including alcoholic beverages, and were encouraged to discuss the use of all medications with the investigator.

Study design

The study design is outlined in Figure 1. Trial candidates were evaluated for inclusion at Visit 1. During this visit, inclusion/exclusion criteria were reviewed; medical history, physical examination, and vital sign information were recorded; and samples were obtained for clinical laboratory testing. After providing informed consent, enrolled patients began daily diary training.

Clinic Visit 2 occurred 1–2 weeks later when overnight polysomnography (PSG) was performed, followed by the Maintenance of Wakefulness Test (MWT). PSGs were scored the following day to identify any co-morbid conditions causing daytime sleepiness, such as obstructive sleep apnea. Patients meeting inclusion criteria entered the 2-week single-blind baseline period and continued taking modafinil at their customary doses (between 200 and 600 mg/day). At this time, patients began taking single-blind placebo sodium oxybate solution in two equally divided doses: the first dose at bedtime, and the second 2.5–4 h later. At the end of the 2-week baseline period (Visit 3), baseline PSG and MWT measures were performed on all patients prior to beginning the treatment phase according to prior double-blind randomization:

- Group 1. *Placebo group*: placebo sodium oxybate + placebo modafinil
- Group 2. *Sodium oxybate group*: sodium oxybate + placebo modafinil
- Group 3. *Modafinil group*: placebo sodium oxybate + modafinil
- Group 4. *Sodium oxybate/modafinil group*: sodium oxybate + modafinil

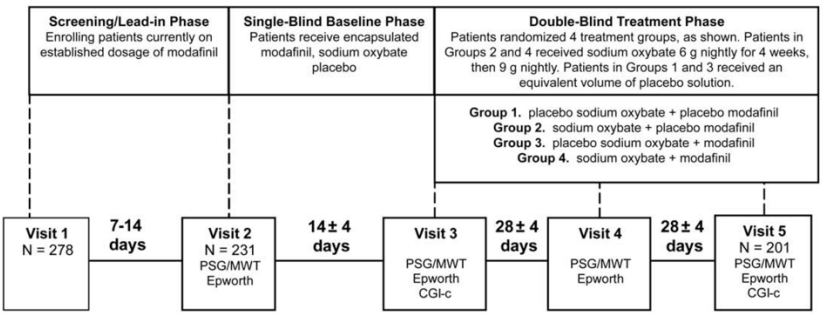

FIGURE 1. Study design. At Visit 1, patients were evaluated for inclusion into the trial. After 1–2 weeks to allow review of hematology and blood chemistry results as well as diary training, patients returned to the clinic for Visit 2. While on stable doses of modafinil, patients underwent a PSG and MWT. The overnight PSG was immediately scored to rule out other conditions that could be primary causes of daytime sleepiness. Subsequently, each patient entered a 2-week baseline phase, remaining on modafinil while receiving placebo sodium oxybate solution in single-blind fashion. At Visit 3, patients were randomized into the four treatment groups as shown. The dose of sodium oxybate (or placebo equivalent) was increased from 6 g nightly to 9 g nightly after week 4. The efficacy and safety measures were performed as indicated, except patient diaries, which were maintained throughout the trial.

Patients randomized to Groups 3 and 4 continued to receive their unchanged modafinil dosage. Patients randomized to Groups 2 and 4 received sodium oxybate at a dose of 6 g nightly, administered in two equally divided doses (at bedtime and 2.5–4 h 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. After 4 weeks, patients returned for PSG and MWT (Visit 4). Patients then continued taking their prescribed modafinil dose; however, the dose of sodium oxybate was increased to 9 g nightly in two equally divided doses. Patients assigned to placebo sodium oxybate increased their placebo solution by an equivalent 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. Patients were permitted to remain on stable doses of drug therapy for cataplexy, if needed, throughout the trial.

Efficacy and safety assessments were performed at Visits 2 through 5 and included the Epworth Sleepiness Scale (ESS) and a nocturnal overnight PSG followed by

MWT. The Clinical Global Impression of Severity (CGI-s) and the Clinical Global Impression of Change (CGI-c) scales were completed at Visits 3 and 5, respectively.

Patient diaries, used to collect information about the incidence of inadvertent daytime naps, trial medication use, concomitant medication use, and adverse events (AEs), were reviewed at each clinic visit.

Safety measures

Safety assessments 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 and clinical chemistry measures and a serum pregnancy test, if applicable. Clinically significant laboratory parameters that were outside the reference range of the central laboratory were repeated. An electrocardiogram was performed at Visit 1 and repeated at Visit 5 if clinically indicated according to the investigator.

All reported AEs were followed until resolution of the event. Any patient who received trial medication during the double-blind phase, but later chose to withdraw from the trial, provided a final measurement of vital signs and blood sample for clinical laboratory tests before discontinuation. If the early termination was due to an AE, the patient was followed until satisfactory resolution of the event occurred.

Statistics

The primary endpoint analysis was conducted on the intent-to-treat (ITT) population. The primary analysis was an ITT analysis at Visit 5. The primary pair-wise comparisons of sodium oxybate and sodium oxybate/modafinil versus placebo were obtained using Dunnet's test. The secondary pair-wise comparisons of modafinil versus placebo did not include an adjustment for multiple comparisons. If data were unavailable for a patient, last observation carried forward analysis was used with last post-baseline observation available for that patient. Two-sided *p*-values were reported, and the level of significance was tested at 0.05.

In the analysis of safety data, AEs were summarized by treatment group, and their incidence was compared using Fisher's exact test. For laboratory data, the mean changes from baseline were compared across treatment groups using ANOVA. 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, Czech Republic, France, Germany, Netherlands, Switzerland, and United Kingdom. The protocol used in this study was approved by the Institutional Review Board/Ethics Committee 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 Helsinki Declaration, revised 1997.

Results

Of 278 patients enrolled in the study, 231 were randomly assigned to one of the four treatment groups. The intent-to-treat (ITT) population consisted of 222 patients who received at least one dose of double-blind medication and provided efficacy data at Visit 3 (baseline), Visit 4, and/or Visit 5. Patient demographics of the ITT population are provided in Table 1.

TABLE 1. Patient demographics by treatment group (ITT population)

	Placebo (*N* = 55)	**Sodium oxybate (*N* = 50)**	**Modafinil (*N* = 63)**	**Sodium oxybate + Modafinil (*N* = 54)**	**Total (*N* = 222)**
Gender, *N*(%)					
Male	24 (44)	26 (52.0)	32 (51)	25 (46)	107 (48)
Female	31 (56)	24 (48.0)	31 (49)	29 (54)	115 (52)
Race, *N*(%)					
White	43 (78)	47 (94.0)	57 (90)	48 (88)	195 (88)
Black	11 (20)	2 (4.0)	5 (8)	5 (6)	21 (11)
Asian	0	1 (2.0)	0	0	1 (1)
Other	1 (2)	0	1 (2)	3 (6)	5 (2)
Age (years)					
Mean (SD)	41.0 (13.4)	35.1 (12.9)	38.9 (15.6)	38.9 (15.9)	38.6 (14.6)
Weight (kg)					
Mean (SD)	84.7 (19.9)	81.8 (17.9)	80.6 (15.1)	79.4 (16.9)	81.6 (17.4)

Polysomnography parameters

After 4 weeks of treatment (Visit 4), there was no significant change in total sleep time in either the sodium oxybate group or the sodium oxybate/modafinil group. The sodium oxybate group demonstrated significant increases in Stage 3 and 4 sleep (p = 0.030) and decreases in REM sleep compared to placebo (p = 0.004) (Table 2). The sodium oxybate/modafinil group demonstrated significant increases in Stage 3 and 4 sleep (p = 0.007) as well as total non-REM sleep (p = 0.042) and delta power (p = 0.012) compared to placebo. The increase in total non-REM sleep closely matched the observed decreases in REM sleep (p = 0.005) and Stage 1 sleep (p = 0.012) for this treatment group versus the placebo group. In addition, there was a significant decrease in nocturnal awakenings in the sodium

oxybate/modafinil group compared to placebo (p = 0.029). In the modafinil group, no changes in sleep parameters were observed.

TABLE 2. Measures of polysomnographic parameters[a,b,c] (Week 4, ITT population; median change)

	Placebo (*N* = 55)	**Sodium oxybate 6 g (*N* = 50)**	**Modafinil (*N* = 63)**	**Sodium oxybate 6 g + Modafinil (*N*= 54)**
Total sleep time (min)				
Baseline	408	427.5	419	407.5
Endpoint	408	412.75	419.75	411.5
Change	−5.5	−5	3	6.5
	–	*NS*	*NS*	*NS*
Total non-REM sleep (min)				
Baseline	327	340	332.75	324
Endpoint	332	346	330	350
Change	0.25	15	2.5	22.5
	–	*NS*	*NS*	p = 0.042
Total REM sleep (min)				
Baseline	73	80.5	78.75	68.5
Endpoint	79	54.25	78.5	54
Change	6.25	−14.5	1.5	−11.5
	–	p = 0.004	*NS*	p = 0.005
Stage 1 sleep (min)				
Baseline	41.5	38.5	40.5	42.5
Endpoint	48.5	31.75	37	29.5
Change	3.25	−9.5	−2	−11.5
	–	*NS*	*NS*	p = 0.012
Stage 2 sleep (min)				
Baseline	252.5	267	241.75	219
Endpoint	241	253	241.5	222.5
Change	−5.25	0.5	−1.5	10
	–	*NS*	*NS*	*NS*

	Placebo (*N* = 55)	Sodium oxybate 6 g (*N* = 50)	Modafinil (*N* = 63)	Sodium oxybate 6 g + Modafinil (*N*= 54)
Stage 3 and 4 sleep (min)				
Baseline	18.5	13.5	29	43.75
Endpoint	24	40	26.5	74.5
Change	0	11	1.5	11.5
	–	*p* = 0.030	*NS*	*p* = 0.007
Delta power (μV^2 /Hz)[d]				
Baseline	77,166	86,801	90,134	85,175
Endpoint	76,620	94,698	81,197	108,548
Change	−2326	10,474	−965	12,292
	–	*NS*	*NS*	*p* = 0.012
Nocturnal awakenings				
Baseline	30	27	30	26.5
Endpoint	26	24.5	33.5	22
Change	−0.5	−1	1	−4
	–	*NS*	*NS*	*p* = 0.029

NS, not significant. [a]Statistical significance was established compared to placebo. [b]Expressed as medians following transformation of non-normal data. [c]Missing data were imputed using last observation carried forward. [d]Median average.

Following 8 weeks of treatment (Visit 5), there were no significant changes in total sleep time noted in any treatment group; however, compared to the placebo group, the sodium oxybate and sodium oxybate/modafinil groups each demonstrated significant increases in total non-REM sleep (for each, $p < 0.001$), specifically sleep Stage 3 and 4 (for each, $p < 0.001$) (Table 3). These increases again corresponded with reciprocal decreases in Stage 1 sleep for the sodium oxybate group ($p < 0.001$) and sodium oxybate/modafinil group ($p = 0.004$) and decreased total REM sleep in both groups (for each, $p < 0.001$). In addition, both groups displayed significant increases in delta power (for each, $p < 0.001$) and significant decreases in the number of nocturnal awakenings in sodium oxybate-treated ($p = 0.008$) and sodium oxybate/modafinil-treated patients ($p = 0.014$). Compared to placebo-treated patients, no changes in any measured parameter were observed in the patients randomized to receive continued modafinil treatment.

TABLE 3. Measures of polysomnographic parameters[a,b,c] (Week 8, ITT population; median change)

	Placebo (*N* = 55)	**Sodium oxybate 9 g (*N* = 50)**	**Modafinil (*N* = 63)**	**Sodium oxybate 9 g + Modafinil (*N*= 54)**
Total sleep time (min)				
Baseline	408	427.5	419	407.5
Endpoint	411	416.75	410.5	416.25
Change	−0.5	−4.5	1	7
	–	*NS*	*NS*	*NS*
Total non-REM sleep (min)				
Baseline	327	340	332.75	324
Endpoint	324	370.75	328.5	365.75
Change	−1	38	−3	42.75
	–	$p < 0.001$	*NS*	$p < 0.001$
Total REM sleep (min)				
Baseline	73	80.5	78.75	68.5
Endpoint	79	43.75	78.5	48.75
Change	10	−38.5	0.75	−26.5
	–	$p < 0.001$	*NS*	$p < 0.001$
Stage 1 sleep (min)				
Baseline	41.5	38.5	40.5	42.5
Endpoint	40.5	20	40.5	25.25
Change	1.5	−16	−0.5	−17
	–	$p < 0.001$	*NS*	$p = 0.004$
Stage 2 sleep (min)				
Baseline	252.5	267	241.75	219
Endpoint	235.5	240.5	251	211.5
Change	−8.25	3.5	−1.75	9.5
	–	*NS*	*NS*	*NS*
Stage 3 and 4 sleep (min)				
Baseline	18.5	13.5	29	43.75
Endpoint	25	74	37	89.25

	Placebo (*N* = 55)	Sodium oxybate 9 g (*N* = 50)	Modafinil (*N* = 63)	Sodium oxybate 9 g + Modafinil (*N*= 54)
Change	0	43.5	0.25	24.25
	–	$p < 0.001$	*NS*	$p < 0.001$
Delta power (μV^2/Hz) [d]				
Baseline	77,166	86,801	90,134	85,175
Endpoint	74,833	105,910	84,911	123,182
Change	−3221	18,443	−639.9	21496
	–	$p < 0.001$	*NS*	$p < 0.001$
Nocturnal awakenings				
Baseline	30	27	30	26.5
Endpoint	30	21	32	18.5
Change	−0.5	−6	1.5	−9.5
	–	$p = 0.008$	*NS*	$p = 0.014$

NS, not significant. [a]Statistical significance was established compared to placebo. [b]Expressed as medians following transformation of non-normal data. [c]Missing data were imputed using last observation carried forward. [d]Median average.

Maintenance of Wakefulness Test and Epworth Sleepiness Score

Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at 8 weeks ($p < 0.001$) once they had been switched to placebo following stable chronic modafinil treatment. Conversely, oxybate/modafinil-treated patients demonstrated a significant increase in MWT sleep latency ($p < 0.001$), compared to baseline modafinil treatment. Patients assigned to receive either modafinil or sodium oxybate alone demonstrated no significant change in MWT sleep latency, compared to baseline modafinil treatment.

Only slight worsening of EDS, as indicated by increased ESS scores, was noted in placebo-treated patients ($p = 0.011$) after discontinuing baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment; however, sodium oxybate-treated patients and sodium oxybate/modafinil-treated patients experienced significant improvements in ESS scores (for each, $p < 0.001$). There was no change in ESS scores in the group maintained on modafinil alone. A detailed discussion of the effects of sodium oxybate, modafinil, and sodium oxybate/modafinil on narcolepsy symptoms in this study has been previously reported [27].

Safety

At least one AE was reported by 151 of 231 patients (65.4%) who entered the double-blind treatment phase of the study. Compared to 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 combination sodium oxybate/modafinil group (78.9%). Among all patients, the most common treatment-emergent AEs were headache (15.2%), nausea (11.7%), dizziness (9.1%), nasopharyngitis (6.1%), vomiting (6.1%), and somnolence (5.6%). Of these, nausea, vomiting, and dizziness were statistically significantly different between treatment groups.

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

The number of patients (*N*) who withdrew from the study early as the result of a treatment-emergent AE was greatest in the sodium oxybate/modafinil group (6) compared to the sodium oxybate (4), modafinil (2), or placebo groups (1). Serious AEs were reported by three patients and included abdominal pain (modafinil group), palpitations (placebo group), and a psychotic disorder due to a general medical condition (narcissistic personality disorder; sodium oxybate/modafinil group); however, the only event considered drug-related was the psychotic disorder. One patient receiving placebo reported a pregnancy (protocol deviation) after completing the trial.

Discussion

A growing body of evidence indicates that nightly administration of sodium oxybate to patients with narcolepsy reduces nocturnal sleep disruption, a common clinical finding in this patient population. The therapeutic effects of sodium oxybate on sleep quality, initially shown to occur clinically in eight patients suffering from insomnia [29] , were later demonstrated in thirty patients with narcolepsy [6,17]. These changes generally coincided with significant improvements in excessive daytime sleepiness and REM-related narcolepsy symptoms [18], and the findings have been replicated in small placebo-controlled clinical trials [19,21].

The results of a placebo-controlled study in 228 narcolepsy patients revealed that the administration of sodium oxybate at doses of 4.5, 6, or 9 g nightly for 8 weeks significantly increased the duration of Stage 3 and 4 sleep, corresponding with significant, dose-related decreases in Stage 1 sleep and REM sleep. Compared to placebo-treated patients, delta power was significantly increased in all dose-

groups [30]. These changes in nocturnal sleep were associated with significant improvements in daytime narcolepsy symptoms [25,26].

The current trial was designed to evaluate the efficacy of sodium oxybate, alone and in combination with modafinil, for the treatment of EDS in patients with narcolepsy. Although compared to placebo, sodium oxybate and modafinil each improved EDS as measured by MWT, and overall clinical condition as measured by clinical global impression of change [27], modafinil alone did not significantly impact nocturnal sleep architecture. In contrast, patients treated with sodium oxybate, either alone or in combination with modafinil, demonstrated significant increases in Stage 3 and 4 sleep after 4 weeks of treatment. In addition, sodium oxybate/modafinil-treated patients demonstrated significant increases in total non-REM sleep and delta power, while Stage 1 sleep and nocturnal awakenings decreased. Following an additional 4 weeks of treatment with sodium oxybate at the 9 g/night dose, the increases in Stage 3 and 4 sleep, total non-REM sleep, and delta power became even more robust and were statistically significant in both sodium oxybate groups, suggesting either a dose-dependent, time-dependent, or dose- and time-dependent effect.

Results from a separate study [unpublished observations] suggest that sodium oxybate may impact sleep in both a dose-dependent and time-on-drug dependent fashion. This study, however, was not designed to characterize any dose-related effects or treatment-duration effects of sodium oxybate on sleep. It remains unclear whether the observed changes in sleep architecture in this study are related to the dose (6 or 9 g/night) or duration (4 or 8 weeks) of sodium oxybate treatment or both. Additionally, it is not known if the observed impact of sodium oxybate on sleep-EEG activity represents pharmacologically-induced alterations in true sleep-related activity, effects representing anesthetic-like changes, or epiphenomenal EEG activity unrelated to either sleep or anesthesia.

The AEs reported by the patients enrolled in the current study were 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 randomized to receive sodium oxybate/modafinil, although this is a common treatment strategy in the clinical setting when neither agent alone adequately addresses EDS [31,32].

Conclusion

This trial represents the first controlled study performed to evaluate sodium oxybate as a single agent for the treatment of excessive daytime sleepiness in narcolepsy. In addition to improvements in EDS, nocturnal PSG data revealed that the nightly administration of sodium oxybate was associated with changes in nighttime sleep suggestive of reduced nocturnal sleep disruption and improved sleep continuity, as indicated by significant decreases in nighttime awakenings and increases in Stage 3 and 4 sleep. While the daytime administration of stimulants improves daytime functioning by increasing alertness, they have not been shown to provide beneficial effects on nocturnal sleep. In addition to improving daytime

symptoms of EDS and cataplexy in patients with narcolepsy, sodium oxybate reduces the nocturnal sleep disruption of narcolepsy.

Disclosures

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Carl S. Hornfeldt, PhD is a consultant to Jazz Pharmaceuticals. Neil Inhaber, MD is an employee of Jazz Pharmaceuticals and own shares of stock and stock options in the company. Daniel Pardi, MS is a former employee of Jazz Pharmaceuticals and owns shares of stock in the company.

All data were collected independently by the respective sites participating in this study. Data entry into the study database was performed by external contract services and the sponsor. Additional independent analysis of the data presented in this manuscript was performed by the authors.

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References

1. Yoss R.E., and Daly D.D.: Criteria for the diagnosis of the narcolepsy syndrome. Proc Staff Meet Mayo Clin 1957; 32: pp. 320-328

2. Fromherz S., and Mignot E.: Narcolepsy research: past, present, and future perspectives. Arch Ital Biol 2004; 142: pp. 479-486

3. Rechtschaffen A., Wolpert E.A., Dement W.C., Mitchell S.A., and Fisher C.: Nocturnal sleep of narcoleptics. Electroencephalogr Clin Neurophysiol 1963; 15: pp. 599-609
4. Plazzi G., Serra L., and Ferri R.: Nocturnal aspects of narcolepsy with cataplexy. Sleep Med Rev 2008; 12: pp. 109-128

5. Montplaisir J., Billiard M., Takahashi S., Bell I.R., Guilleminault C., and Dement W.C.: Twenty-four-hour recording in REM-narcoleptics with special reference to nocturnal sleep disruption. Biol Psychiatry 1978; 13: pp. 73-89

6. Broughton R., and Mamelak M.: Effects of nocturnal gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy–cataplexy. Can J Neurol Sci 1980; 7: pp. 23-31

7. Baker T.L., Guilleminault C., Nino-Murcia G., and Dement W.C.: Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. Sleep 1986; 9: pp. 232-242

8. Folkerts M., Rosenthal L., Roehrs T., Krstevska S., Murlidhar A., Zorick F., et al: The reliability of the diagnostic features in patients with narcolepsy. Biol Psychiatry 1996; 40: pp. 208-214

9. Nishino S., Tafti M., Sampathkumaran R., Dement W.C., and Mignot E.: Circadian distribution of rest/activity in narcoleptic and control dogs: assessment with ambulatory activity monitoring. J Sleep Res 1997; 6: pp. 120-127

10. Nishino S., Riehl J., Hong J., Kwan M., Reid M., and Mignot E.: Is narcolepsy a REM sleep disorder? Analysis of sleep abnormalities in narcoleptic Dobermans. Neurosci Res 2000; 38: pp. 437-446

11. Beuckmann C.T., Sinton C.M., Williams S.C., Richardson J.A., Hammer R.E., Sakurai T., et al: Expression of a poly-glutamine-ataxin-3 transgene in orexin neurons induces narcolepsy-cataplexy in the rat. J Neurosci 2004; 24: pp. 4469-4477

12. Mieda M., Willie J.T., Hara J., Sinton C.M., Sakurai T., and Yanagisawa M.: Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. Proc Natl Acad Sci USA 2004; 101: pp. 4649-4654

13. Zhang S., Lin L., Kaur S., Thankachan S., Blanco-Centurion C., Yanagisawa M., et al: The development of hypocretin deficiency in ataxin-hypocretin transgenic rats. Neuroscience 2007; 148: pp. 34-43

14. Overeem S., Mignot E., van Dijk J.G., and Lammers G.J.: Narcolepsy: clinical features, new pathophysiologic insights and future perspectives. J Clin Neurophysiol 2001; 18: pp. 78-105

15. Hublin C.: Narcolepsy. Current drug treatment options. CNS Drugs 1996; 5: pp. 426-436

16. Rogers A.E., Aldrich M.S., and Caruso C.C.: Patterns of sleep and wakefulness in treated narcoleptic subjects. Sleep 1994; 17: pp. 590-597

17. Broughton R., and Mamelak M.: The treatment of narcolepsy–cataplexy with nocturnal gamma-hydroxybutyrate. Can J Neurol Sci 1979; 6: pp. 1-6

18. Scharf M.B., Brown D., Woods M., Borwn L., and Hirschowitz J.: The effects and effectiveness of γ-hydroxybutyrate in patients with narcolepsy. J Clin Psychiatry 1985; 46: pp. 222-225

19. Scrima L., Hartman P.G., Johnson F.H., and Hiller F.C.: Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy–cataplexy: double blind subjective measures. Biol Psychiatry 1989; 26: pp. 331-343

20. Scrima L., Hartman P.G., Johnson F.H., Thomas E.E., and Hiller F.C.: The effects of γ-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. Sleep 1990; 13: pp. 479-490

21. Lammers G.J., Arends J., Declerck A.C., Ferrari M.D., Schouwink G., and Troost J.: Gamma-hydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. Sleep 1993; 16: pp. 216-220

22. US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42–9.

23. US Xyrem Multicenter Study Group. A 12-month, open-label, multi-center extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep, 2003;26:31–5.

24. US Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med 2004;5:119–23.

25. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med 2005;6:415–21.

26. Xyrem International Study Group. A double-blind, placebo-controlled, study demonstrates the nightly administration of sodium oxybate significantly improves excessive daytime sleepiness in narcolepsy patients taking concurrent stimulant medications. J Clin Sleep Med 2005;1:391–7.

27. Black J., and Houghton W.C.: Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006; 29: pp. 939-946

28. International classification of sleep disorder. 2nd ed. Diagnostic and coding manual. Rochester, MN: American Academy of Sleep Medicine; 2005.

29. Mamelak M., Escriu J.M., and Stokan O.: The effects of gamma-hydroxybutyrate on sleep. Biol Psychiatry 1977; 12: pp. 273-288

30. Black J, Pardi D, Hornfeldt C, Inhaber N. The nightly use of sodium oxybate is associated with significant improvements in nocturnal sleep: a double-blind, placebo-controlled study in patients with narcolepsy. Unpublished manuscript.

31. Wise M.S., Arand D.L., Auger R.R., Brooks S.N., and Watson N.F.: Treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007; 30: pp. 1712-1727

32. Thorpy M.: Therapeutic advances in narcolepsy. Sleep Med 2007; 8: pp. 427-440