The Effects of Sodium Oxybate on Clinical Symptoms and Sleep Patterns in Patients with Fibromyalgia

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ABSTRACT. ***Objective.*** Fibromyalgia (FM) is associated with the sleep phenomenon of alpha intrusion, and with low growth hormone secretion. Sodium oxybate has been shown to increase both slow-wave sleep and growth hormone levels. This double blind, randomized, placebo controlled crossover trial was conducted to evaluate the effects of sodium oxybate on the subjective symptoms of pain, fatigue, and sleep quality and the objective polysomnographic (PSG) sleep variables of alpha intrusion, slow-wave (stage 3/4) sleep, and sleep efficiency in patients with FM.

Methods. Patients received either 6.0 g/day sodium oxybate or placebo for 1 month, with an intervening 2 week washout period. Efficacy measures included PSG evaluations, tender point index (TPI), and subjective measurements from daily diary entries. Safety measures included clinical laboratory values, vital signs, and adverse events.

Results. Twenty-four female patients were included in the study; 18 completed the trial. TPI was decreased from baseline by 8.5, compared with an increase of 0.4 for placebo ($p = 0.0079$). Six of the 7 pain/fatigue scores (overall pain, pain at rest, pain during movement, end of day fatigue, overall fatigue, and morning fatigue) were relieved by 29% to 33% with sodium oxybate, compared with 6% to 10% relief with placebo ($p < 0.005$). Alpha intrusion, sleep latency, and rapid-eye-movement sleep were significantly decreased, while slow-wave (stage 3/4) sleep was significantly increased, compared with placebo ($p < 0.005$). Two of the 5 subjective sleep related variables were significantly different from placebo: morning alertness (improved by 18% with sodium oxybate, compared with 2% for placebo; $p = 0.0033$) and quality of sleep (improved by 33% and 10%, respectively; $p = 0.0003$).

Conclusion. Sodium oxybate effectively reduced the symptoms of pain and fatigue in patients with FM, and dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the nonrestorative sleep characteristic of this disorder. (J Rheumatol 2003;30:1070–4)

Key Indexing Terms:
FIBROMYALGIA SODIUM OXYBATE SLEEP PATTERNS ALPHA INTRUSION
SLEEP QUALITY NONRESTORATIVE SLEEP SLOW-WAVE SLEEP

An estimated 5 to 6 million Americans suffer a constellation of symptoms known as fibromyalgia (FM)[1,2]. The condition is characterized by complaints of overwhelming fatigue and local areas of tenderness, referred to as tender points[3]. Typically, patients report light and/or restless sleep and awaken feeling unrefreshed, with pain, stiffness, and physical exhaustion[4-6]. Patients also commonly complain of migraine, irritable bowel syndrome, and depression[7]. Moldofsky has shown that patients with FM show an alpha electroencephalogram (EEG) frequency (7.5 to 11 Hz) intruding into the encephalogram of non-rapid-eye-movement (non-REM) sleep[4-6]. Although this EEG sleep pattern is a normal part of the EEG pattern of wakefulness, when it occurs extensively in sleep, it is accompanied by daytime complaints of musculoskeletal pain, fatigue, and altered moods[4-6].

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A number of findings suggest a role for the neuroendocrine axis as central to the etiology of FM, including the association with diminished slow-wave sleep and decreased growth hormone secretion. One-third of patients with FM have been reported to show low insulin growth factor (IGF) levels, an indication of low growth hormone secretion[8]. Up to 80% of adult growth hormone is secreted during sleep, primarily during Stage 3 and 4 non-REM (slow-wave) sleep.

Gammahydroxybutyrate (GHB) is a naturally occurring metabolite of the human nervous system, with the highest concentrations found in the hypothalamus and basal ganglia. A commercial form of GHB has been developed as sodium oxybate. In healthy human volunteers, sodium oxybate has been shown to promote a normal sequence of non-REM and REM sleep lasting 2 to 3 hours[9]. Sodium oxybate is the only compound known to cause dose related increases in both slow-wave sleep and growth hormone levels[10]. It has been shown to be safe and effective in the treatment of narcolepsy, reducing daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations[11,12].

We recently reported the effects of sodium oxybate on

the sleep patterns and symptoms of patients with FM in an open label pilot trial evaluating 11 subjects who reported widespread musculoskeletal pain in all 4 quadrants[13]. The results suggested an improvement in subjective assessment of wellness, pain, and fatigue after 1 month of sodium oxybate administration. There was a dramatic reduction in the percentage of non-REM epochs with alpha intrusion.

This double blind, placebo controlled trial was conducted to evaluate the effects of sodium oxybate on the subjective symptoms of pain, fatigue, and sleep quality and the objective polysomnographic (PSG) sleep variables of alpha intrusion, slow wave (stage 3/4) sleep, and sleep efficiency in patients meeting the American College of Rheumatology (ACR) diagnostic criteria for FM[3].

MATERIALS AND METHODS

Study design. This was a double blind, randomized, placebo controlled crossover trial; patients received either 6.0 g/day sodium oxybate or placebo for 1 month, with an intervening 2 week washout period (Table 1). The study consisted of 5 periods: a 2 to 4 week baseline period, 3 nights of pretreatment PSG evaluation, treatment phase I (32 days), a 2 week withdrawal/washout period, and treatment phase II (32 days).

The baseline period included a medical history (including sleep disorders) and physical examination, obtained not more than 4 weeks prior to treatment, and clinical laboratory evaluations, obtained no more than 2 weeks prior to treatment. Examination and tender point assessment was performed by a single board certified rheumatologist, based on the ACR criteria for FM.

Patients completed daily diaries at bedtime and again upon awakening for a minimum of 2 weeks prior to treatment, to assess pain (fatigue levels and location and intensity of pain), sleep (nightly sleep latency, nighttime awakenings, quality of sleep, total sleep time, number of daytime sleepy periods, and levels of daytime alertness), and concomitant medication use.

The pretreatment PSG evaluation included 3 consecutive nights of PSG. The first night was designed to rule out the presence of clinically significant levels of obstructive sleep apnea or periodic limb movements in sleep (PLMS); Nights 2 and 3 were used to establish baseline values. PSG evaluations were scored using the standardized criteria of Rechtschaffen and Kales for sleep staging[14]. The PSG were scored by a blinded board certified technician and a board certified sleep specialist. The number of non-REM sleep epochs with alpha rhythm (7.5 to 11 Hz/s) present was also quantified. Only patients who had alpha intrusion in a mean of at least 30% of non-REM epochs on 2 of the 3 nights were included in the study.

During treatment phase I, patients were randomly assigned in a double blind fashion to receive either placebo or sodium oxybate. Overnight PSG were performed during the first 2 nights of treatment. This was followed by 4 weeks of treatment, with completion of evening and morning daily diaries and weekly clinic visits to assess safety and efficacy. Following the 4 weeks of treatment, patients slept in the laboratory for 2 additional nights of PSG. Tender point evaluations were performed at the end of treatment phase I.

At the beginning of the withdrawal/washout, patients discontinued treatment and underwent 2 additional nights of PSG. This was followed by 10 additional days with no drug treatment; patients continued to complete daily diaries during this period. Following the 10 days, patients underwent 2 consecutive nights of PSG analysis. Tender point evaluations were performed at the end of the washout period.

During treatment phase II, patients were crossed over in a double blind fashion to the opposite treatment (placebo to sodium oxybate and sodium oxybate to placebo) from treatment phase I. Overnight PSG were performed during the first 2 nights of treatment, followed by 4 weeks of treatment with completion of daily diaries and weekly clinical visits to assess safety and efficacy. The last 2 nights of treatment phase II were spent in the sleep laboratory with PSG performed. Tender point analyses were performed again at the end of treatment phase II.

Study medication. Study drug (sodium oxybate or placebo) was administered in 2 nightly divided doses. The first dose was taken at bedtime and the second about 4 h later. Each dose (prepared by a third party to maintain blinding) contained 6 ml of 500 mg/ml sodium oxybate solution diluted in water to total 2 oz, for a total nightly dose of 6.0 g. For placebo, 6 ml was diluted in water to total 2 oz. Patients recorded the dose taken each night. Sodium oxybate and placebo were provided by Orphan Medical Inc., Minnetonka, MN, USA.

Statistical analysis. All computations were performed using SAS version 6.12. Analysis of variance (ANOVA) was used for the crossover design to compare the 2 treatment groups; within-group statistical significance was based on paired t test.

The primary efficacy measures included change from baseline for the tender point index (TPI) and subjective assessments of pain (daily pain, overall pain, pain at rest, and pain during movement) and fatigue (end of day fatigue, overall fatigue, and morning fatigue). Daily pain and fatigue referred to a comparison with their usual level of pain and fatigue, while overall pain and fatigue referral to ratings of symptom severity. Secondary efficacy analyses included change from baseline for alpha intrusion (percentage of non-REM epochs with alpha rhythm), total sleep time, sleep latency, time to wake after sleep onset, sleep efficiency index, percentage of stage 1, 2, and 3/4 sleep, percentage of REM sleep, and number of awakenings.

Baseline 1 was used in the analysis of treatment phase I data, and Baseline 2 was used in the analysis of treatment phase II data. An analysis of the 2 baselines was performed, to determine whether there was any carry-over effect.

For all PSG variables, data points were derived from the mean of the 2 PSG performed at that point. Baseline 1 was the mean of the 2 PSG performed on the 2 nights prior to treatment phase I (Nights 2 and 3 of the pretreatment PSG evaluation). Baseline 2 was the mean of the 2 PSG performed on the last 2 nights of the withdrawal period, prior to treatment phase II. Acute endpoint was the mean of the 2 PSG performed on the first 2 days of each treatment phase. Chronic endpoint was the mean of the 2 PSG performed on the last 2 days of each treatment phase. Withdrawal endpoint was the mean of the 2 PSG performed on the first 2 days after treatment withdrawal (Table 1).

Tender point dolorimetric evaluations were performed during the baseline period (Baseline 1), at the end of the withdrawal/washout period

Table 1. Study design.

Treatment Period	Baseline	Pretreatment PSG	Treatment Phase I			Withdrawal/Washout			Treatment Phase II		
			PSG		PSG	PSG		PSG	PSG		PSG
Duration	2 to 4 weeks	3 nights	2 nights	4 weeks	2 nights	2 nights	10 days	2 nights	2 nights	4 weeks	2 nights
PSG measurement *		Baseline 1**	Acute endpoint		Chronic endpoint	Withdrawal endpoint		Baseline 2	Acute endpoint		Chronic endpoint

* All PSG measurements were a mean of the 2 PSG tests. ** Baseline 1 was the mean of Nights 2 and 3. PSG: polysomnography.

(Baseline 2), and on the last day of each treatment period (Endpoint). The evaluation used the TPI, an objective measure of palpation induced pain in 18 defined points on the body[3]. Induced pain at each site was graded on a severity scale from 0 to 4 (Table 2). The total TPI score can range from 0 to 72.

Subjective measures from the diary entries were evaluated for the week prior to treatment phase I (Baseline 1), the week prior to treatment phase II (Baseline 2), and the last week of each treatment phase (Endpoint), because there was variability in questionnaire completion compliance. In order to be included in the analysis, the diary data had to have 3 of the 7 days completed for that week. Scales for some of the variables were adjusted, so that all scales went from "much worse" (1) to "much better" (5 to 10).

Patient selection. Twenty-four patients were included in the study. To enter the study, patients had to have a confirmed diagnosis of FM according to the ACR criteria[3], including a history of widespread pain in combination with tiredness and pain at 11 or more of the 18 tender point sites; and alpha intrusion in a mean of at least 30% of non-REM epochs on 2 of the 3 nights of the pretreatment PSG evaluation. Only patients who had never taken sodium oxybate were accepted into the study.

RESULTS

Fifty-six patients were screened; 24 patients were enrolled in the study. The great majority of the screen failures were due to patients' unwillingness or inability to withdraw from their current medications. All 24 patients received sodium oxybate; 20 patients received placebo. All patients regularly took both doses of medication or placebo. All 24 patients were female; 23 were Caucasian and one was African-American. Mean age was 48.92 years (range 20 to 69), and was slightly higher in the placebo-sodium oxybate group (52.25 yrs, compared with 45.58 yrs for the sodium oxybate-placebo group). Mean TPI at baseline was 37.17 (range 14 to 53), and was not significantly different between the 2 treatment groups. Six of the patients withdrew, 5 for side effects and one for personal reasons. All dropouts occurred while patients received active medication. No adverse effect was considered serious. One patient experienced headache, 2 had gastrointestinal symptoms, one had anxiety, and the last experienced tingling in face, tongue, and limbs.

Primary efficacy analyses. TPI was decreased significantly by 8.5 from baseline with sodium oxybate, compared with an increase from baseline of 0.4 with placebo ($p = 0.0079$; Table 3). Similar results were seen for both the placebo-sodium oxybate group and the sodium oxybate-placebo group. No carry-over effect was seen when the baselines were compared.

Three of the 4 pain scores and all 3 fatigue scores were increased significantly with sodium oxybate compared with placebo ($p < 0.005$; Table 4). Overall pain, pain at rest, pain during movement, end of day fatigue, overall fatigue, and morning fatigue were relieved by 29% to 33% with sodium oxybate, compared with 6% to 10% relief with placebo. Daily pain showed no change with either placebo or sodium oxybate.

Secondary efficacy analyses. Of the PSG variables analyzed, sodium oxybate significantly decreased sleep latency, alpha intrusion, and REM sleep, and significantly increased percentage of slow-wave (stage 3/4) sleep, compared with placebo after 4 weeks of treatment (chronic endpoint; Table 5). Sodium oxybate also significantly decreased alpha intrusion, to a mean of 25.8% of non-REM epochs compared with placebo ($p < 0.005$).

An analysis of PSG variables for any effect of withdrawal (change from baseline to withdrawal endpoint) showed significant differences between sodium oxybate and placebo for percentage of stage 1 sleep ($p = 0.0136$), percentage of stage 2 sleep ($p = 0.0075$), percentage of REM sleep ($p = 0.0017$), and number of awakenings ($p = 0.0356$), indicating better sleep quality with sodium oxybate.

Two of the 5 subjective sleep related variables analyzed showed a significant difference between sodium oxybate and placebo. The morning alertness score (where 1 = much worse than usual and 5 = much better than usual) was decreased by 0.9 with sodium oxybate, compared with a decrease of 0.1 for placebo ($p = 0.0033$). The quality of sleep the previous night (with 1 = worst possible and 10 = best ever) was increased by 3.3 with sodium oxybate, compared with 1.0 for placebo ($p = 0.0003$).

An analysis of carry-over effect showed significant differences between Baseline 1 and Baseline 2 only for pain at rest ($p = 0.0446$) and pain during movement ($p = 0.0409$) for completed patients overall. No significant differences were seen by treatment sequence.

DISCUSSION

The results of our study demonstrate that sodium oxybate effectively reduces the symptoms of pain and fatigue in FM. The results also indicate a dramatic reduction in the sleep abnormalities (alpha intrusion and diminished slow-wave sleep) associated with the nonrestorative sleep that is a critical feature of this disorder[4-6]. To our knowledge, no other compound has been shown to reduce the alpha sleep anomaly. While this abnormality is not specific to FM and

Table 2. Tender Point Index scale.

Severity Grade	Dolorimeter Reading	Pain	Characteristics
0	0 to 0.9	None	
1	1.0 to 1.9	Mild	Complaint of pain without grimace, flinch, or withdrawal
2	2.0 to 2.9	Moderate	Pain plus grimace or flinch
3	3.0 to 3.9	Severe	Pain plus marked flinch or withdrawal
4	≥ 4.0	Unbearable	Patient is "untouchable" and withdraws without palpation

Table 3. TPI score in completed and intent-to-treat (ITT) patients.

Patients/Treatment Phase	Placebo, No. of Patients (mean ± SD)			Sodium Oxybate, No. of Patients (mean ± SD)		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
Completed Patients*						
Total	17 (40.9 ± 8.2)	17 (41.3 ± 11.5)	17 (0.4 ± 12.4)	17 (40.0 ± 11.9)	17 (31.5 ± 12.3)	17 (–8.5 ± 14.0)**
Treatment phase I	10 (39.8 ± 9.7)	10 (40.2 ± 13.9)	10 (0.4 ± 16.0)	7 (38.4 ± 13.0)	7 (36.3 ± 6.9)	7 (–2.1 ± 12.7)
Treatment phase II	7 (42.6 ± 5.8)	7 (42.9 ± 7.5)	7 (0.3 ± 5.4)	10 (41.1 ± 11.6)	10 (28.1 ± 14.3)	10 (–13.0 ± 13.7)
ITT Patients ***						
Treatment phase I	12 (37.9 ± 9.8)	12 (39.3 ± 12.8)	12 (1.3 ± 14.6)	7 (38.4 ± 13.0)	7 (36.3 ± 6.9)	7 (–2.1 ± 12.7)

* One of the 18 completed patients could not be included in the TPI analysis, since her baseline measurements were taken after treatment had begun. ** p = 0.0079 vs placebo. *** For treatment phase II, ITT patients were the same as the completed patients.

Table 4. Pain and fatigue scores in completed patients.

Variable/Question	Placebo, n = 17			Sodium Oxybate, n = 15		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
Daily pain ("How would you describe your pain today?")*	3.4 ± 1.0	3.6 ± 101	0.2 ± 1.0	3.8 ± 1.0	3.7 ± 0.7	–0.0 ± 1.0
Overall pain ("Rate your overall pain today.")**	3.8 ± 1.1	4.5 ± 2.2	0.7 ± 2.3	4.4 ± 1.1	7.4 ± 1.8	3.0 ± 2.2***
Pain at rest ("Rate your level of pain at rest today.")**	4.0 ± 1.1	4.6 ± 2.2	0.6 ± 2.2	4.6 ± 1.2	7.5 ± 1.7	2.9 ± 2.2***
Pain during movement ("Rate your level of pain when you move today.")**	3.7 ± 1.1	4.4 ± 2.2	0.7 ± 2.2	4.3 ± 1.1	7.2 ± 1.8	2.9 ± 2.1***
End of day fatigue ("Rate your level of pain when you move today.")**	3.6 ± 1.1	4.4 ± 2.4	0.9 ± 2.4	4.4 ± 1.4	7.5 ± 1.9	3.2 ± 2.5***
Overall fatigue ("Rate your overall fatigue for the day.")**	3.6 ± 1.2	4.6 ± 2.4	1.0 ± 2.4	4.4 ± 1.4	7.6 ± 1.8	3.2 ± 2.2***
Morning fatigue ("Rate your morning fatigue.")**	3.7 ± 1.3	4.4 ± 2.3	0.7 ± 2.5	4.3 ± 1.2	7.6 ± 1.8	3.3 ± 2.4***

All results are expressed as the mean score (± SD) for that week. * Adjusted scale of 1 to 5 (1 = much worse than usual; 2 = worse than usual; 3 = the same; 4 = better than usual; 5 = much better than usual). ** Scale of 1 to 10 (1 = worst possible; 10 = best ever). *** $p < 0.005$ vs placebo.

Table 5. Polysomnography (PSG) results in completed patients.

Variable	Placebo, n = 20			Sodium Oxybate, n = 18		
	Baseline	Endpoint*	Change	Baseline	Endpoint*	Change
Total sleep time, min	398.2 ± 34.6	378.4 ± 61.1	–19.8 ± 52.2	388.0 ± 35.7	401.9 ± 36.1	13.9 ± 50.9
Sleep latency	28.3 ± 25.2	30.9 ± 25.6	2.6 ± 11.1	26.0 ± 16.8	18.4 ± 8.3	–7.6 ± 18.2**
Time to wake after sleep onset	53.9 ± 27.4	70.9 ± 47.3	17.0 ± 49.6	63.3 ± 26.6	59.8 ± 34.8	–3.5 ± 41.8
Sleep efficiency index	82.9 ± 7.2	78.8 ± 12.8	–4.1 ± 10.9	81.4 ± 5.9	83.5 ± 7.3	2.1 ± 9.3
Stage 1 sleep (% of total sleep time)	5.8 ± 3.2	7.5 ± 6.9	1.7 ± 7.3	6.0 ± 3.5	5.1 ± 2.7	–0.9 ± 3.1
Stage 2 sleep (% of total sleep time)	52.7 ± 8.4	56.5 ± 9.0	3.8 ± 6.4	56.4 ± 8.6	56.1 ± 5.8	–0.2 ± 11.5
Slow-wave (Stage 3/4) sleep (% or total sleep time)	16.0 ± 7.4	14.1 ± 6.7	–1.9 ± 8.1	14.9 ± 6.5	21.5 ± 7.1	6.6 ± 8.6***
Alpha intrusion (% of non-REM)	37.2 ± 13.0	35.8 ± 14.2	–1.4 ± 9.2	36.9 ± 10.7	25.8 ± 11.8	–11.1 ± 7.1***
REM (% of total sleep time)	25.5 ± 6.6	21.9 ± 6.9	–3.6 ± 6.1	22.7 ± 8.8	17.2 ± 6.5	–5.5 ± 11.4**
Number of awakenings	20.8 ± 8.4	20.4 ± 12.1	–0.4 ± 9.8	21.6 ± 9.6	17.5 ± 8.5	–4.2 ± 8.8

* Chronic endpoint, which was the mean of the 2 PSG performed on the last 2 days of each treatment phase. Results are expressed as mean ± SD. ** $p < 0.05$ vs placebo. *** $p < 0.005$ vs placebo.

its presence has not been distinguished as a cause or effect of the disorder's symptoms, reducing alpha intrusion appears to be a consistent correlate to clinical improvement in the patients in this study.

Previous studies with sodium oxybate in narcolepsy have shown that maximal effectiveness in reducing narcolepsy symptoms is not reached until about 3 months of nightly use[11,12]. In our open label trial, patients who continued taking drug for up to 40 months showed a similar response pattern[13]. In our study, as in some of the placebo controlled narcolepsy studies, ethical considerations and patient compliance issues prevented us from comfortably placing patients on placebo for more than 1 month at a time in the double blind period. In addition,

patients were asked to withdraw from the myriad of medications that they had previously been taking and were limited to concomitant use of nonsteroidal antiinflammatory drugs or acetaminophen compounds. In our pilot study, patients were allowed to continue current therapy even though it was of limited efficacy[13]. Thus, treatment for longer than 1 month, and in combination with other therapies, may result in added benefit in reducing the symptoms of pain and fatigue in FM.

Participants showed a consistent decrease in daily and weekly fatigue and pain, a decrease in TPI, an increase in slow-wave sleep, and a decrease in alpha intrusion when taking sodium oxybate. Patients also reported higher activity levels than normal and felt their symptoms subside. The increase with sodium oxybate in slow-wave sleep in these patients is an important finding, consistent with previous reports in other patient populations[10].

As discussed, sodium oxybate administration increases growth hormone and slow-wave sleep[4-6], both of which are decreased in FM[8,15]. The majority of growth hormone secreted across a 24 hour period occurs during sleep, released in pulses tied to slow-wave sleep. The dosing of sodium oxybate, with 2 doses separated by roughly 4 hours, enables at least 2 pulses of both slow-wave sleep and (assumed) concomitant increases in growth hormone levels.

While the decreased growth hormone levels reported in patients with FM have not been causally related to the disorder, the slow-wave sleep increases seem to occur in conjunction with clinical improvement. Dose selection for this study was based on clinical experience from the open-label study and the effects of sodium oxybate in narcolepsy. Dose-response studies should be a critical part of future corroborative efforts.

Sodium oxybate has been approved for use in the rare condition of narcolepsy. Because of its abuse potential and use in date rape, it is distributed under careful controls. However, despite sodium oxybate's negative reputation, the debilitating effects of FM, the degree of overutilization of the health care system by patients with FM, the lack of effective treatment interventions, and the consistent results from the current double blind and previous open label studies necessitate a close look at this agent as a possible treatment for FM.

One additional benefit of this study may be in identifying an important diagnostic aid. FM has generally been relegated to a diagnosis of exclusion — the key symptoms of pain and fatigue are subjective, vary from day to day, and are not accompanied by abnormalities in clinical laboratory tests. In our pilot open label trial, sodium oxybate had no effect in patients diagnosed with chronic fatigue syndrome[13] — a condition with some symptoms overlapping with FM. In the sleep laboratory, the 2 conditions can be distinguished on the basis of alpha intrusion, which was only present in the patients with FM, suggesting the potential utility of PSG along with ACR guidelines in making a definitive diagnosis of FM. We are aware of no published studies comparing patients with these diagnoses polysomnographically. Patients in our study spent an average of 17 nights in the sleep laboratory over a 3 month period, making this one of the most extensive and comprehensive sleep evaluations ever conducted in FM. The results showed a relative stability of alpha intrusion across nights and a consistent response to sodium oxybate.

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