ORIGINAL ARTICLE

Treatment of the Narcoleptiform Sleep Disorder in Chronic Fatigue Syndrome and Fibromyalgia with Sodium Oxybate

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■ **Abstract:** This study investigates the response of the underlying sleep disorder associated with Chronic Fatigue Syndrome (CFS) and fibromyalgia (FM) to treatment. We retrospectively reviewed 118 cases clinically consistent with CFS or FM, treated in a neurology practice. Abnormal findings on sleep studies and associated human leukocyte antigen markers, and a clinical pattern suggestive of narcolepsy, are present in a high proportion of patients. When considered appropriate based on the clinical picture and test results, treatment with sodium oxybate was offered to these patients. Sixty percent of patients treated with oxybate experienced significant relief of pain, while 75% experienced significant relief of fatigue. We postulate that the response to oxybate in CFS and FM suggests a disturbance of sleep similar to narcolepsy. These findings support this novel approach to intervention and further research. The inability to distinguish CFS and FM by testing and response to treatment suggests that they may represent variations of the same disorder or may be closely related disorders. ■

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INTRODUCTION

Treatment for fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) have largely been unsatisfactory. Recently, pregabalin and duloxetine have received approval for FM, but in practice, relief for patients has generally been limited. Because an underlying mechanism in these disorders is not known, treatment has been empiric. Treatment trials have focused on FM and pain.

The descriptions and definitions of these disorders have substantial overlap,[1,2] and there is controversy about the distinction between them. It is difficult to clearly or objectively identify any abnormality in patients carrying clinical diagnoses of CFS or FM. Various mechanisms have been proposed, including viral infections, immunological causes, dysfunction of the hypothalamic-pituitary-adrenal axis, neurally-mediated hypotension, and nutritional deficiencies[3,4] but despite extensive research, no exact mechanism has been proven, nor has treatment aimed at these mechanisms proven successful. The pathophysiology of CFS and FM are therefore as yet considered unknown, and these disorders are characterized as relatively refractory to treatment.

Traditionally, treatment for classical narcolepsy consisted of daytime stimulant medication. However, more recent recognition of the importance of hypocretin and the disrupted sleep pattern these patients suffer has resulted in another option for therapy. Treatment now focuses on improving sleep, and in particular restorative, deep sleep. Sodium oxybate has been approved for narcolepsy and found to be quite effective, acting through a mechanism of increased stage 3 and 4 deep sleep.[5–9] Conceptually, this approach to treatment is diametrically opposed to previous methods using stimulants, and recent treatment recommendations have included oxybate as primary therapy.

Based on concepts of disrupted nocturnal sleep, some patients with FM have been treated with oxybate. Currently published data show initial promising results,[10,11] but the number of patients treated has been small and the follow-up period has been short. These studies have not included Multiple Sleep Latency Test (MSLT) and human leukocyte antigen (HLA) data. No trial of oxybate has been conducted in CFS as compared with FM. Larger trials in FM, including double-blind placebo controlled studies, are in progress.

This study was undertaken in a general neurology practice and reports the results of treatment in a series of patients with clinical features of CFS and FM. Many of these patients had characteristics diagnostic of narcolepsy. We propose to classify these patients as a narcoleptiform syndrome. The results of clinical evaluation, diagnostic testing, and classification of the narcoleptic features in these patients provided a rationale for treatment with sodium oxybate.

METHODS

This retrospective study was approved by the University of Michigan Institutional Review Board. Subjects were identified from a single practitioner, general neurology practice originally referred for a range of diagnoses. Many cases were referred for consideration of neuromuscular disorders, because of complaints of weakness and myalgia. None of the cases were originally referred for a primary sleep disorder. Only a minority were originally referred for a diagnosis of CFS (3/118, 2%) or FM (33/118, 28%). In some cases, symptoms of CFS or FM were discovered during the review of systems while a patient was being treated for an unrelated disorder.

All cases referred to initiate oxybate over a 5-year period (2003–2008) were identified from the federally mandated registry. Charts that were incomplete at the cutoff date, or that have been treated subsequently, were not included. All diagnoses were made and all treatments were rendered prior to the retrospective analysis, and therefore patient selection, diagnosis, and treatment were not influenced by the study. In the normal course of practice, standard symptom questionnaires had not been employed during treatment, and diagnoses were clinical. Nonetheless, the clinical diagnostic criteria used to establish diagnoses of FM and CFS followed established published guidelines for these disorders (http://www.cdc.gov/cfs/cfsdiagnosisHCP.htm).

Sleep studies were recommended in the course of routine care to all patients in the practice clinically identified with extreme fatigue, disrupted sleep, or sleepiness. These included patients who presented with generalized pain and also had fatigue. Nearly all patients in the practice with severe fatigue did accept recommendations for the sleep studies and had treatment recommended. In many cases, HLA markers associated with narcolepsy were also obtained. Because patients found to have other causes of long-standing fatigue were excluded, all patients remaining met clinical criteria for either CFS or FM.

All patients who had oxybate recommended and were referred to the registry over a 5-year period, and whose records were complete for analysis, were included in this study, even if they subsequently never took the medication. This included patients who were determined to meet criteria for treatment by combined clinical and sleep study criteria, but a small percentage of these were treated based on clinical criteria alone. A patient was referred for treatment with sodium oxybate if the clinical scenario was either classical or suggestive of narcolepsy, although narcolepsy was not suspected initially in any of these cases.

Patients underwent polysomnography (PSG) and MSLT according to standard methodology. Patients who had been recently started on new medications had these discontinued before sleep studies were performed. However, if a patient had been on medications for a prolonged period of time, generally 6 months or greater, no change was made in the regimen. Markers for HLA DQB1-0602 were obtained. Any patients with another cause of hypersomnia such as a restricted sleep schedule, or a cause identified by PSG, such as Obstructive Sleep Apnea or Restless Legs Syndrome, were excluded from the study.

In making the diagnosis of narcolepsy, standard clinical criteria were employed. No single factor, including an isolated finding of rapid eye movement (REM) onset or an HLA marker, was used to make the diagnosis

of narcolepsy. Symptoms such as excessive sleepiness, cataplexy and sleep paralysis, MSLT results, Sleep Onset REM (SOREM), and HLA results were all considered. In the presence of appropriate symptoms, an MSLT with two periods of SOREM was considered diagnostic, but if other classical symptoms were present, a patient was considered to have narcolepsy with only one SOREM. For example, one SOREM would be sufficient if the symptoms were classical and the patient had clear cataplexy. HLA markers were not used as primary diagnostic markers by themselves.

Sodium oxybate is indicated for the treatment of narcolepsy, but not currently indicated for FM or CFS. Patients who were found to have a clinical picture and supportive diagnostic studies that justified the use of oxybate had this medication recommended. In a minority of cases, it was deemed sufficient to recommend oxybate on clinical grounds alone, in keeping with appropriate clinical practice. When appropriate, if they had not previously been used, pregabalin[12] or duloxetine[13,14] were tried first. Most patients with pain had already tried these medications previously. A smaller number tried them *de novo*, and then went on to try oxybate. Pregabalin or duloxetine were not discontinued if they were still in use. Nearly all patients with CFS and FM treated in this practice during this time frame were included in this analysis.

RESULTS

A total of 118 charts were identified for retrospective review. Twenty-five of the patients were male (21%) and 93 were female (79%). The mean age was 53 ± 12 years. Out of 118 patients, 117 (99%) had long-standing fatigue and 82 (69%) had generalized pains and muscle aches in a pattern consistent with FM. Fourteen of 25 male patients (56%) and 68 of 92 female patients (74%) had pain. The pain was typically described as "all over" (as characteristic in FM). Detailed results of diagnostic evaluation in this group have been submitted separately. The results are briefly summarized below.

Approximately 40% of patients met criteria for classical narcolepsy, although most of the remainder had features suggestive of the disorder. Of 92 patients having MSLT, 73 (80%) patients were abnormal, showing shortened time to onset of daytime sleep onset, indicating objective excessive sleepiness. Overall (male and female combined), 36% had at least one period of SOREM. Overall, 43% were positive for HLA DQB1-0602, compared with an 8% average population prevalence in 225 population prevalences ($P < 0.0001$). Sleep architecture was not graded formally. However, qualitatively it was reviewed in all cases, and in nearly every case there was disrupted sleep, poorly maintained sleep, and failure to achieve deeper stages of sleep.

Table 1. Columns 3 and 4 Include Some Who Later Stopped Because of Side Effects, Despite Initial Positive Response

Started Oxybate	Continued on Treatment	Relief of Pain	Relief of Fatigue
85	47 (55%)	50 (59%)	64 (75%)

Of all the patients who started on treatment (column 1), the second column indicates those who remained on treatment. The third and fourth columns indicate those who had relief of pain and fatigue, but some of those eventually discontinued treatment because of side effects, resulting in the lower final number in column 2.

Eighty-five of the 118 patients referred for treatment with oxybate tried at least one dose of the medication.

Of the 85 patients who started oxybate, 37 took it continuously thereafter with good response, 2 took the medication with good response but stopped only because of financial considerations (said they would have stayed on it otherwise), and 8 started the medication, stopped briefly for various reasons, and then resumed the medication. Forty-seven of the 85 (55%) patients were considered to have had a clear positive, efficacious response to the medication, based on their choice to stay on the medication. (Table 1) Altogether, of the 85 patients taking at least one dose of the medication, 50 patients (59%) reported substantial relief of pain and 64 (75%) had significant relief of fatigue. Forty-six (54%) had simultaneous relief of both fatigue and pain.

Of the remainder, five were either lost to follow up or gave no reason for discontinuing the medication, and three stopped because of social issues (related to periods of deep, unresponsive sleep that the medication causes). The remaining 30 discontinued therapy due to other side effects. Note that some patients who have chosen to restart the medication after completion of this study analysis are listed among these 30 who discontinued, rather than among those who restarted. Thus, the listed number of patients remaining on the medication is a conservative number.

Adverse effects are tabulated in Tables 2 and 3. Table 3 lists side effects that patients could accommodate to, that dissipated, or that otherwise did not prevent the patients from continuing on the medication. Table 4 includes side effects that improved at higher doses.

No patients exhibited addiction or physical dependence. Although a specific percentage was not tracked, numerous patients in the practice have stopped the

Table 2. Side Effects Occurring in More than One Patient

Side Effect	Number	Percent
Nausea	15	18
Migraines	13	15
Swelling	11	13
Dyspnea	7	8
Psychiatric/behavioral changes	6	7
Lightheadedness	6	7
Anxiety	6	7
Sleep paralysis	4	5
Numbness, parasthesiae	4	5
Weight loss	4	5
Increased blood pressure	3	4
Polyphagia	2	2
Somnambulation	2	2
Incontinence	2	2
Unmasked sleep apnea	2	2
Polyphagia	2	2

Table 3. Side Effects of Those Who Stayed on Treatment Regardless

Side Effect	Number
Nausea	11
Migraines	8
Swelling	11
Psychiatric/behavioral changes	5
Dyspnea	4
Lightheadedness	3
Anxiety	6
Increased blood pressure	3
Sleep paralysis	1
Polyphagia	1
Somnambulation	2
Sleep apnea	2

Table 4. Side Effects Improving with Increased Dose: One Each Except as Noted

Nausea (3 patients)
Sleep paralysis
Anxiety
Dyspnea
Unsteady gait
Dizziness
Insomnia

Table 5. The Narcoleptiform Syndrome: Common Features Present in These Cases

Long-standing chronic fatigue: either sleepiness or sleep attacks, neuromuscular weariness or fatigability, or both
Generalized muscular and joint pains, and tender points characteristic of FM
Other symptoms of CFS or FM such as memory loss, difficulty with concentration, gastrointestinal disturbances, weight gain, and others tabulated for CFS and FM
Poor sleep, unrefreshing sleep, excessively light sleep, inability to sustain sleep
Associated symptoms of narcolepsy such as cataplexy and sleep paralysis
Disrupted sleep on polysomnogram or lack of deep sleep, *without* other sleep disorders such as sleep apnea or restless legs syndrome
Excessive daytime sleepiness confirmed by MSLT
Sleep onset REM on MSLT
HLA DQB1-0602 present (in some cases)

The more features that are present, the more typical the case.
CFS, chronic fatigue syndrome; FM, fibromyalgia; HLA, human leukocyte antigen; MSLT, Multiple Step Latency Test; REM, rapid eye movement.

medication abruptly for short or long periods of time for various reasons (eg, traveling on vacation or cost issues). None experienced withdrawal symptoms. Generally, significant fatigue or pain recurred after 7 to 30 days, and symptoms gradually returned to baseline in 30 to 90 days. No known cases of abuse occurred.

DISCUSSION

The group of patients clearly had objective hypersomnia as an important finding. Clinically, the original presentations were typical of CFS or FM. Although disrupted sleep has been noted in FM, objective hypersomnia has not clearly been noted in these two groups. This is important regarding current advances in treatment and further research for these patients.

Our patients demonstrated a constellation of consistent findings. The distinction between our patients and CFS or FM is indistinct. When test results were combined with clinical characteristics, these cases were better classified as a "narcoleptiform syndrome" (Table 5). In this syndrome, the fatigue component of the syndrome follows the description of CFS, and the pain component follows the usual description of FM. In addition to hypersomnia, the sleep disorder has many features of narcolepsy, being entirely classical in approximately 40% of cases, and having many of the features in most of the other cases. This provides a rationale for the use of sodium oxybate.

None of these cases had originally been referred to the practice for diagnosis or treatment of narcolepsy or a sleep disorder. Thus, the diagnosis of the sleep disorder or narcolepsy in every case was unanticipated. Furthermore, as only a minority had been referred for treatment of FM and very few had been referred for treatment of fatigue, this study suggests that these disorders are quite prevalent and often under-diagnosed. This finding is in keeping with published data, which suggests that FM and CFS are quite prevalent.

The high response rate to oxybate first and foremost provides a novel and effective treatment intervention for this refractory group of patients. The response rate is very promising compared with previously suggested therapies, as these patients had generally tried duloxet-

ine and pregabalin and failed or achieved an inadequate response. These results expand upon some recent smaller studies, suggesting a role for oxybate in the treatment of FM and further suggesting a role for oxybate in the treatment of CFS. By showing that patients with predominant features of fatigue only (CFS) also respond, this study points to the need for prospective studies in CFS as well. Since this retrospective study was submitted, a recent prospective study has been published which shows similar positive findings with sodium oxybate.[15]

The prospective treatment study recently published does not explore sleep studies or the mechanism of FM. This study provides new information that adds to the understanding of the role of oxybate, and provides a rationale to the use of this medication in FM and CFS. By showing the response to oxybate in the same group of patients who have been demonstrated to have abnormal sleep studies, we provide a physiological rationale for its use and a basis for further study.

The retrospective nature of our study does not allow us to determine if sleep study testing can be used to differentiate and predict response to oxybate in CFS and FM. Our results suggest that this important question should be addressed with a prospective study. Sleep studies may also prove useful in better classifying CFS and FM, for purposes of research into the underlying pathophysiology and etiologies of these disorders. The classification of these disorders may be enhanced by adding sleep studies to their evaluation.

Sodium oxybate produces a high profile of side effects. There is an initial start-up and titration phase during which there may be many side effects, and there are side effects during continuous administration. Some side effects are related to increasing dosage, but paradoxically, some side effects are related to inadequate dosing. Because the medication induces deep sleep, inadequate dosing can produce very unpleasant effects. In addition, some side effects are masked at higher doses when patients fall asleep. For example, some patients report reduced nausea at higher doses when they fall asleep quickly, or reduced episodes of sleep paralysis.

With prolonged use of oxybate, we have observed tachyphylaxis, or possibly a pseudo-tachyphylaxis. After 6 months to 2 years, many patients say the medication "doesn't work as well as it used to"—either because depth of sleep is not fully adequate, or time of sleep is shortened. We believe this may represent the fact that they are simply no longer so extremely tired, they have less accumulated sleep debt. Given the study design, it was not possible to establish correct dosage requirements for these long-term patients. Retitration studies are needed. Whether receptor down-regulation occurs to produce true tachyphylaxis is not known and merits further study. Beneficial responses in some patients may require higher doses than current short-term studies suggest.

For many years, the poor nighttime sleep in FM has been ascribed to the pain. In narcolepsy, the poor nighttime sleep is now recognized as a primary component of the disease itself. The mechanism of action of oxybate is to induce deep sleep. The high response rate in our patients matches the sleep study results, which suggests that a primary narcoleptiform process is present in this group of patients. Thus, the treatment results support the hypothesis that disrupted sleep is part of the primary mechanism and cause of the fatigue and pain, rather than secondary to the pain.

Although sleep onset REM has been considered important for the diagnosis of narcolepsy, effective treatment with oxybate restores deep stages 3 and 4 sleep, not REM. In these cases that we have identified without SOREM that respond to oxybate, the implication may be that CFS and FM are more related to deficiencies of deep sleep. Thus, the short MSLTs may be more significant diagnostically and pathophysiologically than the presence or absence of SOREM. This also merits further study.

Patients with CFS, and with chronic generalized pain suggestive of FM, have approximately the same abnormal rate of excessive daytime sleepiness demonstrated by standardized sleep testing. A significant but similar subset has features suggesting narcoleptic characteristics. Approximately the same response to sodium oxybate occurs with pain and fatigue. Treatment aimed at disrupted sleep seems to be an equally appropriate approach for either diagnosis and fits with our proposed classification as a narcoleptiform syndrome.

REFERENCES

1. Wolfe FSH, Yunus MB, Bennett RM, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis Rheum*. 1990;33:160–172.

2. Centers for Disease Control and Prevention. *Chronic Fatigue Syndrome. The revised case definition*. http://www.cdc.gov/cfs/cfsdefinitionHCP.htm (accessed on October 24, 2009).

3. Centers for Disease Control and Prevention. *Chronic Fatigue Syndrome. Possible causes*. http://www.cdc.gov/cfs/cfscauses.htm (accessed on October 24, 2009).

4. Gur A, Oktayoglu P. Central nervous system abnormalities in fibromyalgia and chronic fatigue syndrome: new concepts in treatment. *Curr Pharm Des*. 2008;14:1274–1294.

5. U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multi-center trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep*. 2002;25:42–49.

6. U.S. Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. *Sleep Med*. 2004;5:119–123.

7. 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;6:415–421.

8. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med*. 2005;1:391–397.

9. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29: 939–946.

10. Scharf MB, Hauck M, Stover R, et al. Effect of Gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. *J Rheumatol*. 1998;25:1986–1990.

11. Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. *J Rheumatol*. 2003;30:1070–1074.

12. Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6 month double-blind, placebo controlled trial with pregabalin. *Pain*. 2008;136:419–431.

13. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004;50:2974–2984.

14. Arnold L, Rosen A, Pritchett Y, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*. 2005;119:5–15.

15. Russell IJ, Perkins AT, Michalek JE; Oxybate SXB-26 Fibromyalgia Syndrome Study Group. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum*. 2009;60:299–309.