Illustration by: Anthony Di Lauri

Sleep Apnea in Patients With Fibromyalgia: A Growing Concern

Patients with fibromyalgia have a tenfold increase in sleep-disordered breathing, including obstructive sleep apnea. Proper diagnosis and treatment will improve health and quality of life for fibromyalgia patients.

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Fibromyalgia (FM) is a widespread pain and fatigue syndrome without a known cause. The prevalence of FM ranges from 2% to 3% of the general population, with women affected six to nine times more frequently than men.[1] It is estimated that the prevalence increases in women as they age, from 4% at age 20 to 8% by age 70.[1-3]

Most patients with FM complain of hurting all over—from head to toe. The neck, back, hips, and shoulders are typically prominent sites of pain. Patients also will frequently complain of poor sleep, burning and numb sensations, dry eyes and mouth, temperature sensitivity (feeling cold), headaches, fatigue, dizziness, abdominal and bladder problems, sensitivities to medications, restless leg syndrome, jaw discomfort, and difficulties with mood and memory.

From its earliest description in the literature, FM has been recognized as more than a pain syndrome. Researchers' understanding that FM involves central nervous system sensitization and deep sleep dysregulation have changed the focus of FM diagnosis and treatment. Revised diagnostic criteria are illustrated in Table 1. As such, clinicians have begun to recognize that the treatment of sleep and fatigue comorbitities should be a major focus in the management of FM patients. The objective of this article is to review current diagnosis and treatment options for sleep-related problems in patients with FM, including a case presentation representative of a common FM patient.

Sleep Disturbances

According to a recent article, sleep and fatigue symptoms have surpassed pain as the most prominent complaints in FM patients (see Table 2).[4] It is now known that FM

Table 1. American College of Rheumatology New Diagnostic Criteria for Fibromyalgia

The American College of Rheumatology (ACR) has recommended a revised Fibromyalgia Diagnostic Criteria (FDC), which does not include the tender point examination and puts more emphasis on the broad spectrum of symptoms commonly seen in fibromyalgia patients.[1]
Widespread Pain Index (WPI) 0-19
Ask about pain in 19 body regions
Symptom Severity Scale (SS) 0-12
Symptom *domains* 3 (0-3 severity): (fatigue, cognition, tired)
0=None, 1=Slight/mild, 2=Moderate, 3=Severe
Somatic *symptoms* (0-3 scale) based on number of other symptom domains:
0=None, 1=Few, 2=Moderate, 3=Many
ACR 2010 FDC confirmed diagnosis if: WPI ≥7 + SS ≥5 OR WPI 3-6 + SS ≥9

Source: Wolfe F, Clauw DJ, Fitzcharles MA et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62(5):600-610.

Table 2. Summary of Most Prominent Complaints in Fibromyalgia Patients

Symptoms	Mean Severity (SD)
Morning stiffness	7.2 (2.5)
Fatigue	7.1 (2.1)
Nonrestorative sleep	6.8 (2.0)
Pain	6.4 (2.0)
Forgetfulness	5.9 (2.7)

Note that pain is rated below fatigue and sleep.
Source: Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord*. 2007;8:27.

patients suffer from a litany of sleep issues including nonrestorative sleep with alpha-wave intrusions, insomnia, restless leg syndrome, hypersomnia such as narcolepsy, and obstructive sleep apnea (OAS).

Perhaps the most common sleep problem seen in patients with FM is nonrestorative sleep. The majority of patients with FM will have alpha-wave intrusions during deep sleep. It is thought that this phenomenon contributes to sleep complaints among patients with FM. In the past, the diagnosis of alpha-wave intrusions could be very time consuming, with researchers counting the intrusions by hand over many hours. Today, diagnostic approaches, including the use of quantitative electroencephalography (qEEG), can easily demonstrate alpha-wave intrusions in deep sleep (see Figure 1).[5]

Figure 2 shows alpha-wave intrusion during delta waves on a sleep hypnogram from an overnight sleep study using polysomnography (PSG) in a patient with FM. More than 90% of patients with FM will have alpha-wave intrusions during their sleep and it is thought that this phenomenon contributes to pathology and complaints in patients with FM. Recent therapeutic approaches that target this phenomenon, such as the γ-aminobutyric acid (GABA)-type B agonist, sodium oxybate, has been shown to reduce alpha-wave intrusions, as well as improve symptoms of pain and fatigue.[6,7]

In addition to alpha-wave intrusion that may impair the restorative aspect of sleep, FM patients usually have diminishment of the overall amount of deep sleep. In the normal population, slow-wave sleep (SWS) should account for 20% to 25% of sleep, but in the FM population it is typically much less. In Figure 3, a normal sleep hypnogram demonstrates normal deep sleep predominantly in the first 5 hours of sleep as compared to a FM patient who does not enter deep sleep for any significant period of time and has multiple unexplained arousals.

Patients with sleep disordered breathing (SDB) also can present with a number of complaints, including drowsiness, inability to sleep, cognitive dysfunction, fatigue, mood complaints, and decreased libido. A

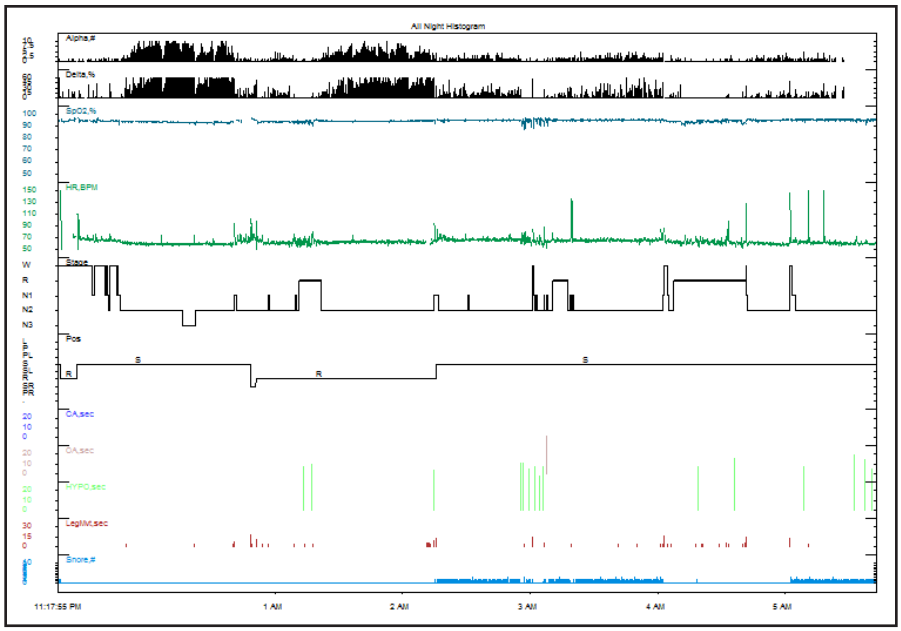


Figure 1: Alpha wave intrusion (top line) clearly demonstrated by quantitative electroencephalography analysis can be seen in parallel with delta waves (second line) in this patient with fibromyalgia.

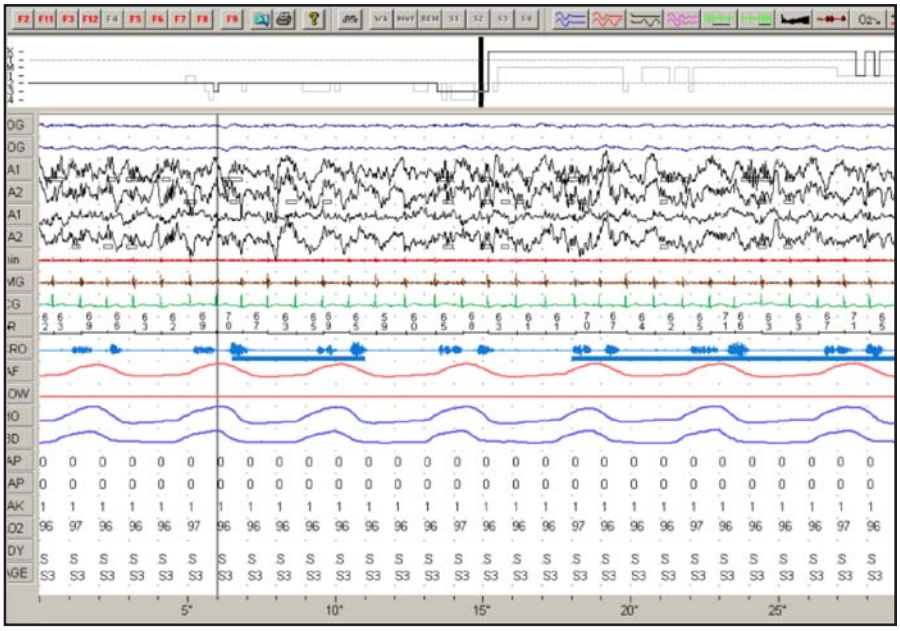


Figure 2. Alpha waves superimposed on delta waves during slow-wave sleep in a patient with fibromyalgia.

small case study demonstrated that treatment of SDB could improve symptoms in patients with FM.[8] We also know that disruption of deep sleep in healthy individuals can predispose them to increases in pain perception and cognitive difficulties. A number of smaller trials have shown that when deprived of SWS, healthy volunteers developed pain and cognitive dysfunction similar to that seen in the FM population; findings that support the association between dysfunctional sleep and FM.[9]

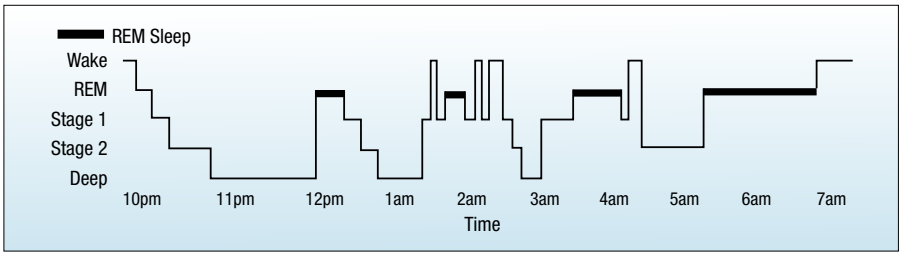
Given the plethora of complaints common in both patients with FM and SDB, there has been new interest in ruling out SDB in patients with FM. Since we know that patients with FM can have poor quality sleep, the identification of a treatable sleep disorder such as SDB is something that can greatly benefit this patient population.

Patients with FM and SDB have added risk factors—prescription of sedative or narcotic agents, which can cause or worsen SDB. With the airway blocked, air cannot reach the lungs and oxygen levels drop. This causes the brain to slightly wake up; this is referred to as a microarousal. These brief repeated arousals cause sleep to be nonrestorative and put stress on the heart and other organs.

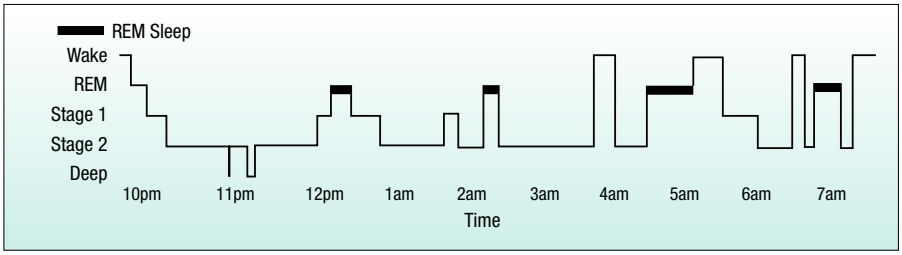
Sleep Apnea

One of the more serious SDBs is OSA. The condition is characterized by loud, frequent snoring and involves the partial or complete collapse of the airway during sleep. With OSA, muscles in the throat start to relax during sleep, which makes it more likely for the airway to collapse. An apnea is described as a cessation of airflow >10 seconds. A hypopnea is typically defined as a decrease in airflow of at least 30% associated with a decrease in oxygen saturation of >4%. Episodes can occur hundreds of times in one night. A large neck (greater than 18 inches in men or 16 inches in women), body mass index (BMI) >35 kg/m^2, a retrusive jaw, or large tonsils in children can predispose patients to OSA.

Obstructive sleep apnea can cause excessive daytime drowsiness, which can affect performance at work and quality of life. When oxygen levels drop, numerous physiologic changes occur, including elevated cortisol levels, hyperglycemia, insulin resistance, and increase in sympathetic tone with increased heart rate and blood pressure. Because of this, OSA has been linked to a number of medical conditions, including high blood pressure, stroke,



Sleep stage diagram of a normal night's sleep.



Sleep stage diagram of a person with fibromyalgia.

Figure 3. A normal sleep hypogram showing 25% deep sleep in the first 5 hours of sleep (above) and in in a fibromyalgia patient (below), where there is no deep sleep.
REM, rapid eye movement

heart attack, atrial fibrillation, gastroesophageal reflux, diabetes, and glaucoma. Problems controlling weight, mood and memory problems, as well as diminished libido, also are common symptoms associated with OSA.

The incidence of moderate and severe OSA in the general population is estimated to range from 5% to 7% in men and 2% to 4% in women.[10] However, in women who have been diagnosed with OSA, the incidence of FM is tenfold higher than in the normal population, indicating a profound association between SDB and FM.[11]

Diagnosis: Sleep Testing

To evaluate for OSA, an overnight polysomnography that identifies the apnea-hypopnea index (AHI) should be ordered. An AHI of 5 to 15 times per hour is considered mild; more than 15 times per hour is considered moderate; and more than 30 times per hour is considered severe. Overnight PSG will also look for problems in sleep architecture such as decreased deep sleep or the presence of alpha-wave intrusions, which are common sleep findings in the FM population. Problems such as low-sleep efficiency and increased period limb movements also can be readily ascertained during a standard PSG, possibly leading to treatment interventions that can improve sleep quality in patients with FM.

Most sleep physicians will initiate therapy for patients with AHI in the moderate category. Patients who have mild sleep apnea and are drowsy or who have comorbid conditions (eg, hypertension, atrial fibrillation) also may be candidates for intervention.

Treatment of SDB in Fibromyalgia

The treatment of SDB in patients with FM may at times be more difficult than in the typical OSA population due to pain, hypervigilance, and non-restful sleep. For patients with severe OSA (AHI >30), the only therapy that is indicated is continuous positive airway pressure (CPAP). The CPAP machine stops the cycle of OSA by delivering a stream of compressed air via a hose to a nasal pillow, nose mask, full-face mask, or hybrid, thereby creating a pneumatic splint that keeps the airway open. This promotes unobstructed breathing and often reduces and/or prevents apneas and hypopneas. Advancements in CPAP technology (eg, improvements that allow ambient air to be humidified without manual adjustment) can significantly reduce the amount of condensation that accumulates in the tubing that connects the machine to the mask.

Today, most CPAP machines are equipped with expiratory pressure relief that maintains positive pressure during inspiration, but reduces pressure during exhalation. The reduction in pressure during exhalation makes it easier for the patient to breathe. The titrated pressure is the pressure of air at which most (if not all) apneas and hypopneas have been prevented, and it is usually measured in centimeters of water (cm/H_2O). A typical CPAP machine can deliver pressures between 4 and 20 cm/H_2O.

The expiratory pressures usually are prescribed by the sleep physician. The newest autotitrating machines (AutoPAP), will titrate pressure according to snore vibrations and other internal algorithms that can help provide an adequate amount of pressure support when patients need more pressure—such as during rapid eye-movement (REM) sleep, when muscle relaxation is increased, or while the patient is supine. The AutoPAP also reduces the pressure automatically when the patient is in a light sleep or in a lateral decubitus position, greatly reducing the amount of awakenings patients experience as a result of therapy.

There also has been an increase in the types of mask interfaces available for those who require CPAP. These include small nasal pillow CPAP masks that resemble nasal cannulas (Swift FX for Her, ResMed). For patients who breathe through their mouths while sleeping and require a full-face mask, there are mouth-nasal pillow combinations that help to reduce claustrophobic complaints (Mirage Liberty,

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tapentadol. In principle, these symptoms may particularly appear in the clinical setting: miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of Overdose

Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe NUCYNTA®:

Instructions for Use

Patients should be advised NUCYNTA® should be taken only as directed and to report episodes of breakthrough pain and adverse experiences occurring during therapy to their physician. Individualization of dosage is essential to make optimal use of this medication. Patients should be advised not to adjust the dose of NUCYNTA® without consulting their physician *[see Dosage and Administration (2) in full PI]*. Patients should be advised that it may be appropriate to taper dosing when discontinuing treatment with NUCYNTA® as withdrawal symptoms may occur *[see Drug Abuse and Dependence]*. The physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Misuse and Abuse

Patients should be advised that NUCYNTA® is a potential drug of abuse. Patients should protect NUCYNTA® from theft, and NUCYNTA® should never be given to anyone other than the individual for whom NUCYNTA® was prescribed *[see Warnings and Precautions]*.

Interference with Cognitive and Motor Performance

As NUCYNTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles *[see Warnings and Precautions]*.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Nursing

Patients should be advised not to breast-feed an infant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Monoamine Oxidase Inhibitors

Patients should be informed not to take NUCYNTA® while using any drugs that inhibit monoamine oxidase. Patients should not start any new medications while taking NUCYNTA® until they are assured by their healthcare provider that the new medication is not a monoamine oxidase inhibitor.

Seizures

Patients should be informed that NUCYNTA® could cause seizures if they are at risk for seizures or have epilepsy. Such patients should be advised to use NUCYNTA® with care *[see Warnings and Precautions]*. Patients should be advised to stop taking NUCYNTA® if they have a seizure while taking NUCYNTA® and call their healthcare provider right away.

Serotonin Syndrome

Patients should be informed that NUCYNTA® could cause rare but potentially life-threatening conditions resulting from concomitant administration of serotonergic drugs (including Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors and tricyclic antidepressants) *[see Warnings and Precautions]*.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs as there is a potential for interactions *[see Drug Interactions]*.

Alcohol

Patients should be advised to avoid alcohol while taking NUCYNTA® *[see Drug Interactions]*.

Medication Guide

See Medication Guide (17.10) in full PI. Revised: November 2010

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ResMed). In addition, there are masks that fit over the entire face, similar to a windshield (Fit Life, Respironics).

For patients with mild sleep apnea or moderate-severe OSA, oral appliance therapy with mandibular advancement (OAT) can be efficacious and is usually well tolerated (TAP 3, Dental Arts Laboratories; SomnoDent, SomnoMed). Oral appliances typically reduce AHI by 50% and are sometimes better tolerated than CPAP. One drawback is that oral appliances can exacerbate tempromandibular joint (TMJ) symptoms, a frequent comorbidity in patients with FM. These devices work by advancing the mandible, which opens the airway, and are constructed specifically for the patient by dentists who are board-certified by the American Academy of Dental Sleep Medicine.

At times, patients may exhibit an elevated AHI while supine that may resolve when they assume a side-lying position. This is referred to as positional apnea. In these cases, instead of placing patients on CPAP, an ergonomic approach or a positional pillow (Sona Pillow) may be an effective, well-tolerated, and cost-efficient alternative.

A new and exciting experimental strategy for OSA that is currently under investigation is hypoglossal nerve stimulation (HGNS). A number of companies, including Apnex, ImTherma, and Medtropic, are already well into Phase II clinical trials. HGNS involves implantation of a neurostimulator in the anterior chest wall connected to a respiration sensing lead and a nerve cuff electrode that is attached to the hypoglossal nerve in the submandibular region. When stimulated, the genioglossus muscle will contract and significantly increase the size of the retropharynx, thereby improving airflow and reducing apneas and hypopneas. After implantation, a programming system allows fine tuning of the device and a therapy controller will allow patients to activate the system prior to sleep and then turn it off when awake. This may end up being a viable option in the FM patient who requires treatment for OSA, but is intolerant of CPAP.

Conclusion

Fibromyalgia is the most common widespread pain condition in the world. The majority of patients with FM will have prominent sleep complaints that often surpass their pain complaints. A better understanding of sleep problems associated with FM, as well as improved testing and treatment, will enable the pain practitioner to care for patients and improve their symptoms, health, and quality of life. The tenfold increase of SDB in the FM patient population is not well understood, but is readily amenable to testing and the myriad treatment options now available. ■

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Case Study: Patient With Fibromyalgia And Sleep Apnea

History

A 54-year-old woman with widespread pain, fatigue, and insomnia presents to the healthcare provider's office with complaints of excessive daytime drowsiness. The patient noted that she developed chronic widespread pain and fatigue following routine gynecologic surgery to treat endometriosis in 1993. Since that time, she has been seen by numerous specialists, including rheumatologists, neurologists, urologists, pain specialists, and gastroenterologists.

Past Medical History

The patient was initially diagnosed and treated for systemic lupus erythematosus, although testing was inconclusive and she has never developed any classic manifestations of the disease. She initially rated her pain on a visual analog scale (VAS) as 9 of 10, but now says that it is about 4 of 10. She has many syndromes associated with fibromyalgia (FM), including irritable bowel syndrome, irritable bladder, migraine headaches, fatigue, temporomandibular joint (TMJ) pain, restless leg syndrome (RLS), non-refreshing, nonrestorative sleep, and myofascial pain.

A neurologist has managed the patient's migraines with the use of intramuscular lidocaine and corticosteroid injections. To stop the migraine, the patient takes a triptan agent, usually with good success. Her past medical history is negative for cervical spinal trauma or psychosexual trauma.

Medication History

The patient's medication history includes failed treatment with duloxetine (Cymbalta) and milnacipran (Savella). Pregabalin (Lyrica) and gabapentin therapy produced weight gain and somnolence. Trazodone therapy caused excessive daytime sleepiness, zolpidem (Ambien) caused some complex sleep behaviors, and diazepam caused depression. Pramipexole (Mirapex) has helped her RLS and pain. Benadryl, which helps with sleep, exacerbates her RLS.

The patient's current medication history includes tramadol 100 mg per night (Ultram); acetaminophen and hydrocodone (Vicodin), used sparingly; pramipexole 1.5 mg per night; clonazepam 0.5 mg per night (Klonopin); sertraline 25 mg/day (Zoloft); Tylenol PM, and zolpidem as needed.

The patient is a busy executive for a nonprofit organization who neither smokes nor drinks. She has a brother diagnosed with obstructive sleep apnea (OSA), but no family history of FM or RLS.

Medical Examination

On presentation, the patient complains of excessive daytime drowsiness. Epworth Sleepiness Scale is elevated at 21. Fatigue Severity Scale is elevated at 50. The patient admits to problems with drowsiness during the day that affects her ability to function, including falling asleep at work and meetings, having near car accidents, and having to take frequent naps during the day.

Table 1. Physical Examination Tests and Results

Test	Results
Vital statistics	
BP	120/70 mmHg
HR	70 beats/minute
BMI	28 kg/m^2
Neurologic examination	Normal
Mini-mental status	Alert and oriented. Higher cortical functions intact.
Cranial nerves	Cranial nerves II through XII are within normal limits.
Motor	5/5 strength in all extremities. Normal tone and bulk. No excess or paucity of movement. No pronation or fixation.
Sensory	Normal to light touch, pinprick, joint position sense, vibration. No cortical sensory loss is present.
Coordination	Reveals no dysmetria or dysdiadochokinesis.
Deep tendon reflexes	Reflexes are equal and symmetric throughout. There are no pathological reflexes elicited. Toes are downgoing.
Gait	Normal. Negative Romberg. Normal tandem.
ENT	Turbinate hypertrophy, Mallampati I, small neck, nonretrusive jaw.
Musculoskeletal	12/18 specific tender points for FM.

BMI, body mass index; BP, blood pressure; ENT, otolaryngeal examination; FM, fibromyalgia; HR, heart rate

Circadian rhythm is quite variable due to her work schedule and multiple sleep issues, but she usually goes to bed around 1:00 AM, wakes up at 5:30 AM, and uses sleep aids. She has been told that she stops breathing at night. She has gastroesophageal reflux, and wakes up with headaches. Her RLS is managed well with pramipexole 1.5 mg taken at bedtime and she wears a bite guard for her TMJ. There is no obvious evidence of hypersomnia or narcolepsy. Sleep hygiene is poor. Table 1 provides results from the physical examination and Figure 1 illustrates the results of the sleep hypnogram.

Diagnosis and Treatment Plan

Based on the results of physical examination and polysomnography (PSG), the patient was diagnosed with FM, RLS, insomnia, and

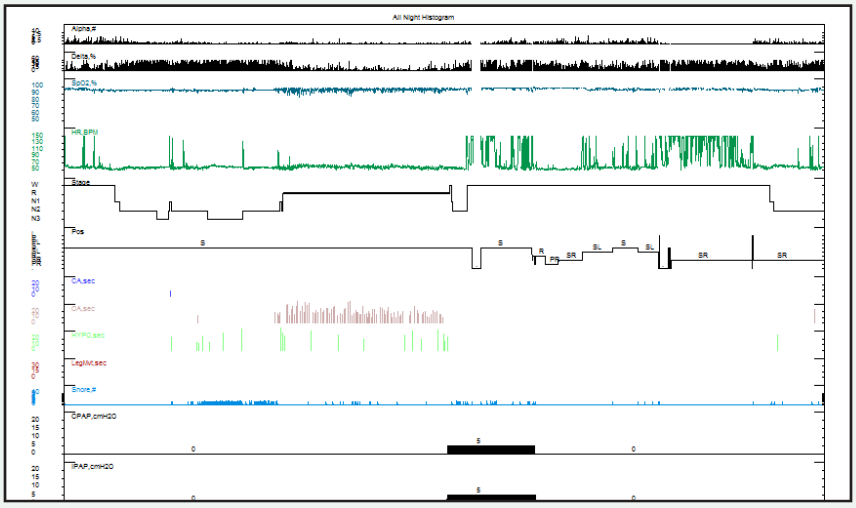

Figure 1. Sleep hypnogram of patient with fibromyalgia. Notice that alpha-wave intrusions were not seen during deep sleep; rather, severe obstructive sleep apnea with oxygen desaturation was found. A brief CPAP trial was intolerable and she remained awake the rest of the night.

severe OSA. The patient was started on a regimen of sodium oxybate 3 g per night (Xyrem), given in divided doses, to help treat the pain, fatigue, and sleep problems associated with FM. ~~Recently approved by the FDA~~, sodium oxybate has been shown in large Phase III trails to reduce pain and fatigue, and improve sleep and function in patients with FM.[1]

Since the patient is intolerant to continuous positive airway pressure (CPAP) devices, the severe OSA was treated with an oral appliance therapy with mandibular advancement. The patient was continued on pramipexole for RLS and told to avoid Benadryl. The patient was instructed on good sleep hygiene practices and was given benzodiazepine sparingly to treat insomnia.

Follow Up

The oral appliance therapy was effective for OSA in this patient, as evidenced by nocturnal pulse oximetry findings and resolution of sleepiness, but her TMJ was exacerbated. It was recommended that the patient consider turbinate surgery and retrial of CPAP (with or without sodium oxybate) to assist with pain and sleep. Her RLS remained and was treated with pramipexole and avoidance of Benadryl. Her insomnia improved, but sleep hygiene remains a persistent issue. The patient had a significant reduction in fatigue and nonrestorative sleep while on moderate doses of sodium oxybate (3 mg/night); higher doses produced increase side effects that outweighed any additional sleep benefit.

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Dr. Rosenfeld has no financial information to disclose.

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