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Sleep Disorders and Fibromyalgia

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Abstract Disordered sleep is such a prominent symptom in fibromyalgia that the American College of Rheumatology included symptoms such as waking unrefreshed, fatigue, tiredness, and insomnia in the 2010 diagnostic criteria for fibromyalgia. Even though sleep recording is not part of the routine evaluation, polysomnography may disclose primary sleep disorders in patients with fibromyalgia, including obstructive sleep apnea and restless leg syndrome. In addition, genetic background and environmental susceptibility link fibromyalgia and further sleep disorders. Among nonpharmacological treatment proposed for sleep disturbance in fibromyalgia, positive results have been obtained with sleep hygiene and cognitive-behavioral therapy. The effect of exercise is contradictory, but overweight or obese patients with fibromyalgia should be encouraged to lose weight. Regarding the approved antidepressants, amitriptyline proved to be superior to duloxetine and milnacipran for sleep disturbances. New perspectives remain on the narcolepsy drug sodium oxybate, which recently was approved for sleep management in fibromyalgia.

Keywords Sleep · Fibromyalgia pathophysiology · Treatment · Sleep disorders · Fibromyalgia · Fibromyalgia criteria · Amitriptyline · Cognitive-behavioral therapy · Pain · Nonrestorative sleep · Genetics · Polysomnography · Inventory · Sleep quality · Medical Outcomes Study Sleep Scale · Fibromyalgia Impact Questionnaire · Sleep Assessment Questionnaire · Patient-Reported Outcome Measurement Information System

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Introduction

Poor sleep quality has been shown to be associated with pain in patients with fibromyalgia [1], and whenever sleep is perceived as restful, patients report substantial improvement in their daytime symptoms [2, 3•, 4]. A night of poor sleep has been considered as a predictor of a more painful day, and a more painful day has been reported to be followed by a night of poorer sleep [5].

In the study that established the 1990 fibromyalgia criteria, 73% to 85% of patients reported fatigue, sleep disturbance (nonrestorative sleep or insomnia), and morning stiffness [6], and a classic epidemiologic research article indicates that up to 65.7% of patients complain about nonrestorative sleep [7]. More recent cross-sectional [8] and longitudinal [9] studies conducted in larger fibromyalgia populations confirm that more than 90% of patients report sleep problems such as difficulty in falling asleep, nighttime awakenings, and unrefreshing sleep.

The diagnosis of fibromyalgia increases the chance of persistent symptomatology of pain, fatigue, sleep disturbance, anxiety, and depression up to a 7-year follow-up [10]. In contrast, only 35% of the community with chronic widespread pain still remained symptomatic up to a 27-month period of a study [11].

The impact of sleep on fibromyalgia symptomatology [2, 4, 9, 12–15] may have an immunological background, as shown in Table 1, because interleukin-1β and tumor necrosis factor-α share influences on neuroendocrine, autonomic, limbic, and cortical areas of the central nervous system (CNS) that regulate sleep [16, 17]. Conversely, the development of chronic pain may influence sleep through physical and functional modifications of the CNS. The increased sympathetic activity [18], underactivated hypothalamic-pituitary-adrenal axis [19–21], and the re-

Table 1 Influence of cytokines on the sleep induction action of type 1 interleukin and tumor necrosis factor-α

Cytokine action	TNFα	IL- 1B
Anti-inflammatory	Inhibition by IL-10	Inhibition by IL-1R1, IL4, IL-10, and IL-13
Proinflammatory	Stimulation by IFNγ and IL-1R1	NR

IL interleukin; *IL-1R1* type 1 interleukin-1 receptor; *IFN* interferon; *NR* not reported; *TNFα* tumor necrosis factor alpha

lease of proinflammatory cytokines from glial cells [22, 23] have been proposed as the underlying mechanisms of disordered sleep in fibromyalgia. Notwithstanding, the reciprocal relationship between sleep disturbance and pain in fibromyalgia [9, 24–28] still remains controversial in terms of the impact of such an interaction in fibromyalgia manifestations [29].

New Criteria for the Diagnosis of Fibromyalgia

In 2010, the American College of Rheumatology proposed symptom-based practical criteria for clinical diagnosis of fibromyalgia [30••] to complement the 1990 criteria, which were based on widespread pain complaint and specific tender points [6]. The new criteria recognize a wide spectrum of manifestations and severity of symptoms that can affect different individuals and the same individual throughout time. A widespread pain index (WPI) of 19 areas of the body and a symptom severity score (SSS) including specifically fatigue, waking unrefreshed, and cognitive symptoms are considered together with further somatic symptoms. For the diagnosis of fibromyalgia, it is required a WPI score of at least 7 and an SSS of at least 5 or a WPI of 3 to 6 and an SSS of at least 9. The SSS scale also provides follow-up information in patients with current or previous diagnosis (Table 2) [30••].

Nonrestorative Sleep and Fibromyalgia

Disordered sleep is a multidimensional construct, comprising complaints such as delay of sleep onset, difficulty in staying asleep, waking too early, and nonrestorative sleep (waking feeling unrefreshed) [3•]. Compared with healthy control patients, most patients with fibromyalgia perceive their sleep to be of poor quality, reporting it as nonrestorative [13, 31], and feel unrefreshed upon awakening [8]. Among the array of manifestations of fibromyalgia, nonrestorative sleep is consistently ranked as a highly bothersome symptom of the disease, together with pain, morning stiffness, and fatigue [4, 31, 32]. Self-reports of unrestful sleep or feeling unrefreshed upon awakening and throughout the day may result in poor quality of sleep even with normal sleep duration [13, 33]. However, due to the subjective nature of nonrestorative sleep perception there is no standardized way of defining or evaluating its daytime or nighttime consequences in terms of mood, anxiety, depression, fatigue, concentration, and performance [34].

In addition, depression and reported sleep impairment contribute with fatigue in these patients [12], but because psychological factors are associated both with sleep quality and pain, they may confound the relationship of both conditions.

Primary Sleep Disorders and Fibromyalgia

Nonrestorative sleep has received increased attention in the literature and has been associated not only with fibromyalgia, but also with chronic fatigue syndrome, insomnia, and obstructive sleep apnea [13]. On the other hand, primary sleep disorders, such as obstructive sleep apnea [35] and restless legs syndrome [13, 36], have been reported among patients with fibromyalgia, and a genetic study found common genetic characteristics between fibromyalgia and narcolepsy [37].

Female sex remains a predictor of fibromyalgia, and the average age of onset is between 30 and 50 years, dropping off after 80 years [38]. The prevalence in middle-aged and overweight women [38] may contribute to further sleep disorders [39–41], such as sleep apnea [13, 42] and inspiratory airflow limitation with arousals [43].

Pathogenesis of Nonrestorative Sleep In Fibromyalgia

Early small, uncontrolled family studies provided evidence for familial aggregation of fibromyalgia [27, 44, 45] that were confirmed by larger and controlled studies that suggest the influence of both environmental and genetic aspects [46].

Neuroendocrine Response to Environment

Among environmental factors, chronic stress has been considered the underlying factor for the neuroendocrine dysfunctions described in fibromyalgia, such as hyperactive and hyporeactive hypothalamic-pituitary-adrenal axis, which can directly or indirectly affect the adjustment of cortisol response and lead to variable manifestation of the characteristic symptoms of fibromyalgia, including fatigue, pain, depressed mood, and nonrestorative sleep [19–21]. Alterations in HPA axis function also

Table 2 American College of Rheumatology 2010 criteria for fibromyalgia

A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:

1) WPI ≥7 and SSS score ≥5; or WPI 3–6 and SSS score ≥9

2) Symptoms have been present as a similar level for at least 3 months

3) The patient does not have a disorder that would otherwise explain the pain

1. WPI

Number of areas where the patient has pain (score: 0–19)

•Shoulder girdle, left	• Hip (buttock, trochanter), left	•Jaw, left	•Upper back
•Shoulder girdle, right	•Hip (buttock, trochanter), right	• Jaw, right	•Lower back
•Upper arm, left	•Upper leg, left	•Chest	•Neck
•Upper arm, right	•Upper leg, right	•Abdomen	
•Lower arm, left	•Lower leg, left		
•Lower arm, right	•Lower leg, right		

2. SSS score

Sum of the severity of the three symptoms, plus the extent (severity) of somatic symptoms in general (final score: 0–12)

2.1 Severity somatic symptoms

•Fatigue

•Waking unrefreshed

•Cognitive symptoms

For each of the three symptoms above, indicate the level of severity over the past week using the following scale: 0 = no problem; 1 = slight or mild problems; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe: persuasive, continuous, life-disturbing problems

2.2 Somatic symptoms in general

Considering somatic symptoms in general, indicate whether the patient has no symptoms (0), few symptoms (1), a moderate number of symptoms (2), or a great deal of symptoms (3)

•Chest pain	•Blurred vision	•Constipation	•Fatigue/tiredness
•Fever	•Dry eyes	•Diarrhea	•Insomnia
•Frequent urination	•Easy bruising	•Dry mouth	•Depression
•Headache	•Hair loss	•Heartburn	•Dizziness
•Muscle pain	•Hives/welts	•Loss of appetite	•Seizures
•Muscle weakness	•Itching	•Nausea	•Hearing difficulties
•Numbness/tingling	•Rash	•Loss of/change in taste	•Nervousness
•Shortness of breath	•Sun sensitivity	•Vomiting	•Wheezing
•Pain/cramps in the abdomen	•Oral ulcers	•Irritable bowel syndrome	•Ringing in ears
•Painful urination and bladder spasms	•Raynaud's phenomenon	•Pain in the upper abdomen	•Problems with thinking or remembering

SSS Symptom Severity Scale; *WPI* widespread pain index

(*Data from* Wolfe et al. [30••])

may provide an explanation for the observation of subnormal growth hormone (GH) secretion in some patients with fibromyalgia, which may contribute to the development of impaired cognition, fatigue, muscle weakness, and decreased exercise tolerance [19]. Given that GH and somatomedin C are necessary for the repair of muscle microtrauma, sleep disturbances may impair the healing of muscle tissue damage, thereby prolonging the transmission of sensory stimuli from damaged muscle tissue to the CNS and enhancing the perception of muscle pain [47]. In turn, this enhanced pain may contribute to increase in sleep disturbance, thereby maintaining the patient's fatigue and continuing the inadequate muscle tissue repair [48].

There also are evidences that patients with fibromyalgia have abnormal heart rate variability and an altered sympathetic response to upright posture and tilt table testing, suggesting a persistently hyperactive sympathetic nervous system (including during sleep) [18] that is hyporeactive to stress [22].

Environmental triggers that may be involved in the pathophysiology of fibromyalgia include mechanical/physical trauma or injury and psychosocial stressors (for review, see Bradley [48]). Commonly reported

physical traumas include acute illness, physical injury, surgery, and motor vehicle accidents. Commonly reported psychosocial triggers include chronic stress, emotional trauma, and emotional, physical, or sexual abuse. Coincidently, physical and psychosocial stress also may increase sleep complaints in middle-aged women [49].

Genetic Aspects

Population-based studies with twins suggest genetic influence on sleep may play a role in the pathogenesis of nonrestorative sleep in fibromyalgia [50•]. Evidence for familial aggregation of fibromyalgia suggests that inherited factors may be involved in pain sensitivity, mood disorder, anxiety disorder, eating disorders, irritable bowel syndrome, and migraine exhibited by the patients [46].

Preliminary genetic studies revealed possible association of fibromyalgia with genetic polymorphisms in monoamine-related genes, including the serotonin-2A receptor gene (*HTR2A*) [51, 52], which is also a candidate gene for obstructive sleep apnea [53]. The serotonin transporter gene regulatory region (5-HTTLPR) is controversially associated with personality trait in fibromyalgia [54, 55], and an s-allele of the 5-HTTLPR is frequent in patients suffering from insomnia [56]. The dopamine D4 receptor gene, also associated with personality trait in fibromyalgia [57], has been related with sleep attacks in Parkinson's disease [58]. Furthermore, a functional Val158Met polymorphism (in which substitution of valine [Val] to methionine [Met] at codon 158 results in reduction in the activity of the catechol-O-methyltransferase [COMT] enzyme, which metabolizes catecholamines) is associated with human pain sensitivity [59] in several pain conditions, including fibromyalgia [60]. Interestingly, mechanisms involving COMT contribute to interindividual differences in brain alpha oscillations, which are functionally related to executive functions in healthy individuals, and predict stable and frequency-specific interindividual variation in brain alpha oscillations in wakefulness, rapid-eye-movement (REM) sleep, and non-REM sleep [28].

In a retrospective study, Spitzer and Broadman [37] showed that 43% of 118 patients meeting standard clinical criteria for fibromyalgia or chronic fatigue syndrome had positive HLA DQB1*0602 genotype and characteristics of narcolepsy. Most of these patients presented highly fragmented sleep in conjunction with neuromuscular fatigue or generalized pain, which are objective evidences of hypersomnia.

Diagnosis

Polysomnography

Even though sleep disturbance often is considered a secondary phenomenon in fibromyalgia and complete sleep testing is not part of the routine evaluation, polysomnographic investigation of nonrestorative sleep may disclose unknown or unheeded factors for patients who have undergone unsuccessful treatment [61].

Specific alterations in sleep architecture have been documented, particularly sleep fragmentation known as alpha electroencephalography (~10 Hz) sleep disorder [13, 62–65]. This pattern of sleep fragmentation, known as phasic alpha sleep activity, has been observed in 50% of patients [64], and subsequently was interpreted as a cyclic alternating pattern that correlates to the severity of symptoms such as unrefreshing sleep, pain, fatigue, and depressed mood in fibromyalgia [62].

Regarding actigraphy monitoring, patients with fibromyalgia alone show similar levels of daytime activity as well as disturbed sleep with significantly increased levels of activity at night compared to normal control patients. Patients with fibromyalgia and comorbid depression also have reduced daytime activity and significantly increased daytime sleeping compared to control patients, as well as more sleep interruption and movement during the night [66].

Inventories

According to specific guidelines proposed by The German Society of Sleep Research and Sleep Medicine, the modern approach to nonrestorative sleep prioritizes identification and restoration of daytime functioning rather than nighttime aspects of nonrestorative sleep [61], and several instruments have been proposed to evaluate aspects of nighttime sleep experiences or morning or daytime restoration and nonrestorative sleep [34].

Regarding fibromyalgia, among the 10 subscales of the classical Fibromyalgia Impact Questionnaire (FIQ), the items 16 ("How tired have you been?") and 17 ("How have you felt when you get up in the morning?") score aspects related to sleep quality from 0 to 10, higher scores indicating a greater impact [67]. The Sleep Assessment Questionnaire, the first specific inventory for sleep in fibromyalgia, has been proposed by Moldofsky's group [68] and evaluates the concept of nonrestorative sleep with a domain score.

In the Patient-Reported Outcome Measurement Information System (PROMIS) network, the sleep disturbance scale focuses on perceived sleep quality, sleep depth and

restoration, and perceived adequacy of and satisfaction with sleep. The wake disturbance scale covers the levels of waking alertness, sleepiness, and function. These domains have been used to define standardized outcome measures to assess fibromyalgia [29] and provide identification of key domains related to overall sleep–wake function [69].

Notwithstanding, for the assessment of the impact of pain on sleep in fibromyalgia, the Medical Outcomes Study Sleep Scale (MOS-SS) may represent the best choice [32]. This 12-item questionnaire about initiation and maintenance of sleep, respiratory problems during sleep, amount of sleep, perceived adequacy of sleep, and daytime somnolence [70] also has been used to evaluate fibromyalgia-related sleep problems and the impact of treatment with pregabalin on these symptoms throughout time in a randomized, double-blind, placebo-controlled, phase 3 trial of pregabalin [71]. In addition, for the assessment of modification of sleep symptoms in patients with fibromyalgia in a 4-week recall period and to capture the effect of treatment on fibromyalgia manifestations, the use of the Jenkins Sleep Scale also has been proposed [3•, 72]. In comparison to the Medical Outcome Study (MOS) Sleep Questionnaire, this four-item instrument captures the varying pain severity and day-to-day variation in sleep quality [73•].

Management of Sleep Disturbances in Patients with Fibromyalgia

The European League Against Rheumatism (EULAR) 2008 recommendations for fibromyalgia treatment included nine evidence-based directions for its management. The second recommendation refers to the need of optimal pharmacological and nonpharmacological treatment of several domains, including sleep disturbance. Even though the primary objective is pain control, the recommended approaches for the management of fibromyalgia syndrome produce some of the effect on sleep quality [74••].

Nonpharmacological Approach

Education is a key point in treatment, and sleep hygiene should be encouraged by every professional responsible for their care [75]. However, it has been demonstrated that instructions alone are more effective when combined to cognitive-behavioral therapy (CBT) with regards to sleep quality evaluated by both subjective and objective results [76]. In addition, it has been shown that CBT can be a tool in the management of sleep dysfunction in both adults and children with fibromyalgia. The positive results also are achieved in other aspects of behavior, such as attention disturbance and daily functioning [77]. Notwithstanding, the EULAR 2008 recommendations pointed out beneficial results of CBT only on function and pain.

The effect of exercises in the quality of sleep in patients with fibromyalgia is contradictory. Recent Spanish trials of aquatic exercises in warm water confirmed improvement in sleep quality evaluated by the Pittsburgh Sleep Quality Index when combined techniques included aerobic, strength, and relaxation exercises or Tai Chi, but not when stretching was used [78]. On the other hand, a recent review concluded that aerobic exercises had no positive effects on sleep in patients with fibromyalgia; yet, there was a reduction in pain, fatigue, and depressed mood. Therefore, prescription should consist of land-based or water-based exercises with slight to moderate intensity two or three times per week for at least 4 weeks [79].

A 12-week trial of Tai Chi versus stretching and education showed that at 12 weeks, the Tai Chi group had greater mean improvement in sleep quality as measured by the change in the Pittsburgh Sleep Quality Index score than the control group and that it persisted at 24 weeks [80]. Despite the support for the use of nonpharmacological interventions such as CBT and exercises, van Koulil et al. [81] noted that their effects often are limited, positive outcomes disappear in the long term, and treatment outcomes vary considerably among individuals. It was suggested that efficacy may be enhanced by offering tailored treatment approaches at early stages of the disease.

Obesity is clearly related with poorer sleep quality. A study showed that lesser sleep duration and poorer sleep efficiency in patients with fibromyalgia were associated with a greater body mass index. Patients with fibromyalgia who are overweight or obese should be encouraged to lose weight [40].

A recent systematic review of randomized trials with acupuncture treatment of fibromyalgia included only seven trials. However, none of the trials showed sleep improvement in those patients [82].

Pharmacological Approach

Despite the fact that patients with fibromyalgia have poor sleep quality, several prescription and over-the-counter drugs may be responsible for sleep disturbance, and physicians ought to be aware of their use. Some examples are anticonvulsants (phenytoin and lamotrigine), β-blockers (atenolol, metoprolol, and propranolol), antipsychotics (sulpiride), and NSAIDS (indomethacin, diclofenac, and naproxen) [83]. Tables 3, 4, and 5 show medications used to treat conditions related or not to sleep that can interact with sleep [84].

Table 3 Common medications that can interact with sleep: psychostimulants, hypnotics, and antiparkinsonians

Class	Drug	Polysomnography	Clinical effect on sleep
Psychostimulants	Methylphenidate	↓ REM and ↓SWS; ↑ Sleep latency	↓ Sleep continuity. Tolerance/dependence can develop with long-term use
	Modafinil	↓ Total sleep time and ↓REM	↓Wakefulness; ↑ alertness. No potential for drug dependency or rebound
Hypnotics	Benzodiazepines	↓ Sleep latency, ↓REM, and ↓SWS; ↑ stage 2 sleep and ↑spindle density	↑ Sleep continuity; sedation, dependence, and rebound of insomnia if withdrawn. Shorter-acting drugs cause sleep disruption in the 2nd part of the night
	Nonbenzodiazepines (zolpidem)	↓ Sleep latency and ↓REM	↑ Sleep continuity; no residual sedation (eszopiclone is a longer-acting agonist with no effect on REM or SWS)
	Melatonin	↓ Sleep latency	↑ Sleep continuity
Antiparkinsonians	Levodopa (low dose)	↑ SWS; may ↓ REM	Improve sleep
	Levodopa (high dose)	↑Spindle activity and ↑REM density	↓ Sleep continuity; nightmares and insomnia
	Ropinirole	↓ Sleep latency; no effect on REM or SWS	↑ Sleep continuity
	Pramipexole	↓ REM	Sedation
	Benztropine	↓ REM; may ↑ SWS	↓ Sleep continuity; cognitive impairment
	Selegiline	↓ REM sleep	↓ Sleep continuity; insomnia
	Amantadine	NR	Insomnia

↓—decrease; ↑—increase; *NR* not reported; *REM* rapid eye movement sleep; *SWS* slow-wave sleep

Amitriptyline and other tricyclic antidepressants (TCAs) have been used as the cornerstone of drug therapy in fibromyalgia for 20 years and may provide long-term benefit for improving sleep, but not for reducing pain beyond 1 month. Among the antidepressants approved by EULAR 2008 for the treatment of

Table 4 Common medications that can interact with sleep: antidepressants

Drug class	Drug	Polysomnography	Clinical effect on sleep
Tricyclic antidepressants	NS	↓ Sleep latency and REM; no effect on SWS	↑ Sleep continuity; may ↑ periodic limb movements (tertiary tricyclics more sedative than other tricyclics)
	Amitriptyline and imipramine	↑ Sleep latency and REM density; ↓ REM	↑ Sleep continuity and sedation (Nortriptyline: less sedation and ↓ REM
Selective serotonin reuptake inhibitors	Citalopram and escitalopram	Citalopram: ↓ REM sleep. Escitalopram: smaller effect	No effect on sleep latency or sleep continuity; vivid dreams
	Fluoxetine, sertraline, and paroxetine	↑ Sleep latency; ↓ REM and may ↓ SWS	↓ Sleep continuity
Serotonin norepinephrine reuptake inhibitors	Venlafaxine	No effect on sleep latency; ↓ REM and SWS	↓ Sleep continuity; does not induce insomnia
	Duloxetine	↑ REM latency and duration	NA
	Milnacipran	↑ Sleep duration and efficiency and stage 2 sleep; ↓ sleep latency and REM	NA
Monoamine oxidase inhibitors	NS	↓↓ REM sleep	Phenelzine: ↓ Sleep continuity; insomnia
Dopamine reuptake inhibitor	NS	↑ REM; no effect on sleep latency	Bupropion has no effect on sleep continuity; less effect on periodic limb movements, insomnia, and nightmares
Atypical antidepressants	Trazodone	↓ Sleep latency; no effect on REM or in SWS	↑ Sleep continuity; sedation, impaired performance, and priapism

↓—decrease; ↑—increase; *NA* not available; *NS* none specified; *REM* rapid eye movement sleep; *SWS* slow-wave sleep

Table 5 Other common medications that can interact with sleep

Drug class	Drug	Polysomnography	Clinical effect on sleep
Antipsychotics	Haloperidol chlorpromazine	NR	↑ Sleep continuity; sedation
	Aripiprazole	NR	Insomnia
	Clozapine and olanzapine	↓ Sleep latency and ↓REM sleep	↑ Sleep continuity, sedation, and impaired performance
	Quetiapine	↓ REM sleep	↑ Sleep continuity, sedation, and impaired performance
	Risperidone	↓ REM and ↑SWS	↑ Sleep continuity, sedation
	Lithium	↓ REM; ↑ REM latency and ↑SWS	↑ Sleep continuity, sedation, and impaired performance
Antiepileptics	Phenytoin	↓ Sleep latency and ↓ REM; ↑SWS;	May ↓ sleep continuity; sedation
	Carbamazepine	↓ Sleep latency and ↓ REM; ↑ SWS	↑ Sleep continuity
	Barbiturates (phenobarbital)	↓ Sleep latency and ↓REM; ↑spindle density; may ↓ SWS	↑ Sleep continuity, sedation, and impaired performance
	Topiramate	NR	Sedation
	Valproic acid	NR	↑ Sleep continuity. New-generation antiepileptics are less sedating
	Tiagabine	May ↓ sleep latency; ↑SWS; no effect on REM	↑ Sleep continuity
	Gabapentin/pregabalin	↑ REM and SWS	↑ Sleep continuity
Histamine antagonists	First-generation H1-antagonists	↓ Sleep latency; may ↓ REM	↑ Sleep continuity; sedation
	H2-antagonists	Famotidine: ↓ sleep latency. Cimetidine: ↑ SWS	Somnolence in elderly patients and in patients with renal impairment
Cardiovascular medications	β-Blockers (*propranolol/ metoprolol)*	↓ REM sleep	↓ Sleep continuity; fatigue, insomnia, and nightmares
	α1-antagonists	NR	Transiently sedation
	α2-Agonist (c*lonidine)*	↓ REM; ↑ SWS	↑ Sleep continuity; sedation and nightmares
	Angiotensin-converting enzyme inhibitors	NR	Insomnia and nightmares
Hypolipidemic drugs	Statins	NR	Insomnia
	Fibrates	NR	Sleepiness and drowsiness
Anti-inflammatories	Aspirin and ibuprofen	↓ SWS	↓ Sleep continuity
	Corticosteroids	↓ SWS and ↓REM; ↑ Stage 2 sleep;	↓ Sleep continuity; insomnia and nightmares
Opiates	Morphine	↑Sleep latency, ↑SWS, and ↑REM; sleep fragmentation	Acute use: sedation, impaired performance, respiratory depression. Chronic use: insomnia, tolerance, and withdrawal-related sleep disturbances
	Tramadol	↑ REM and SWS	NR

↓—decrease; ↑—increase; *NR* not reported; *REM* rapid eye movement sleep; *SWS* slow-wave sleep

fibromyalgia, amitriptyline proved to be superior to duloxetine and milnacipran in improving sleep disturbances [85•]. A meta-analysis found large effect sizes of TCAs and small effect sizes of serotonin–norepinephrine reuptake inhibitors (such as milnacipran and duloxetine) for reducing sleep disturbances, whereas no effects were found for serotonin–norepinephrine reuptake inhibitors or monoamine oxidase inhibitors [86].

Regarding dopaminergic agonists, a trial with pramipexole did show improvement in pain, fatigue, function, and global status in patients with fibromyalgia. These patients did not have the sleep attacks or hallucinations commonly described by patients taking pramipexole at a dosage of up to 1.5 mg orally three times a day for the treatment of Parkinson's disease [87]. Terguride, a partial dopamine agonist that presents beneficial effects on

cervical spine symptoms in fibromyalgia, has not been studied in sleep [88].

Among anticonvulsants, the γ-aminobutyric acid (GABA) analogue pregabalin has been effective in decreasing sleep latency and enhancing slow-wave sleep in patients with altered sleep architecture [86]. In fibromyalgia, doses at 300 and 450 mg daily were associated with significant improvement in sleep quality [89, 90].

Sodium oxybate is a type B receptor agonist of γ-hydroxybutyric acid (a metabolite of GABA that increases dopamine in the brain) that is approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

By reducing physiological sleep instability, this drug has been proven to facilitate slow-wave sleep and reduce wake periods after sleep onset [91••]. Russel et al. [92], with the use of sodium oxybate, 4.5 or 6.0 g per night, showed significant reduction in patient-reported sleep disturbance in fibromyalgia as measured by mean change from baseline to week 14 on the Jenkins Sleep Scale. However, no significant changes were observed in the Functional Outcomes Sleep Questionnaire in either group.

Finally, regarding other therapeutic options in fibromyalgia, a controlled study provided evidence of the effect of tramadol plus acetaminophen in the improvements in sleep adequacy and sleep duration, but the use of this synthetic opioid-receptor agonist has not been effective for other parameters of sleep as analyzed by the MOS sleep questionnaire [93]. With respect to benzodiazepines (agonists of the GABA-A receptor), only five drugs have been approved for the management of insomnia: estazolam, flurazepam, quazepam, temazepam, and triazolam. Even though there is no specific orientation regarding the use of benzodiazepines in the management of sleep in fibromyalgia, in case of prescription, the lowest effective dose should be indicated to minimize side effects such as rebound insomnia and anterograde amnesia [83]. Nonbenzodiazepine hypnotics also act on the GABA-A receptor and, while helpful in initiating and maintaining sleep and reducing daytime tiredness, do not provide restorative sleep or reduce pain [13]. Zolpidem, but not zopiclone, was reported to improve sleep in fibromyalgia [94]. Melatonin has a variety of beneficial effects on the treatment of fibromyalgia, as shown through small open studies [95, 96]. Even though multiple actions, including modulation of the sleep/wake cycle, benzodiazepine-like effects [97], synchronization of circadian rhythms [98], and anti-inflammatory effect [99], may account for the potential benefits of melatonin, it was not included in the EULAR recommendations for the treatment of fibromyalgia [74••, 100].

Conclusions

Fibromyalgia is a common pain condition with a complex pathophysiology that contributes to a vast array of manifestations, among which, sleep abnormalities have pronounced evidence. Due to the subjective nature of this condition, instruments have been developed to assess fibromyalgia sleep status. Even though the primary outcome of the approved therapeutic strategies is pain control, these nonpharmacological and pharmacological recommended approaches for the management of fibromyalgia have been proven effective in the management of sleep disturbance.

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•• Of major importance

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Heading

Fibromyalgia (Mario F. P. Peres, Section Editor).