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Review Article

Correlations between Sleep Disturbances and Pain in Fibromyalgia: An Updated Review

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Abstract

Fibromyalgia (FM) is a common condition characterized by chronic musculoskeletal pain. Sleep disturbances, such as reduction of Slow Wave Sleep (SWS) and alpha wave intrusion in non-Rapid Eye Movement (non-REM) sleep, are a main feature of FM and are related to alterations of central nervous system, autonomic nervous system and endocrine system. Improving sleep quality can significantly reduce patient reported symptoms. Polysomnographic findings support the hypothesis of a vicious circle of sleep disturbances, impaired sympathetic and nociceptive pathways and chronic pain. Despite better understanding of underlying pathophysiological processes, there is currently limited data about effectiveness of available pharmacological therapies for sleep. All the three drugs currently licensed by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treating FM (duloxetine, milnacipran and particularly pregabalin) can improve sleep quality in these patients. Other drugs, like gabapentin, sodium oxybate, cyclobenzaprine and cannabinoids, can be beneficial for FM-related sleep disturbances, but more evidence needs to be collected for their use to be possibly recommended. Non-pharmacological treatments aimed at improving sleep hygiene can still be considered the mainstay intervention for sleep disturbances in FM, relying on an all-round assessment of patients' clinical history and comorbidities. Further studies are needed to fully investigate efficacy and safety of promising therapies.

Keywords: Fibromyalgia; Sleep; Non-restorative sleep; Polysomnography; Pain management; Autonomic nervous system

Abbreviations: FM: Fibromyalgia; EEG: Electroencephalography; EMG: Electromyography; EOG: Electrooculography; REM: Rapid Eye Movement; SWS: Slow Wave Sleep; CAP: Cyclic Alternating Pattern; PLM: Periodic Limbs Movements; CNS: Central Nervous System; fMRI: functional Magnetic Resonance; 5-HT: 5-Hydroxytryptamine; HR: Heart Rate; $HF_{RR:}$ High Frequency component of RR variability; GH: Growth Hormone; IGF-1: Insulin-like Growth Factor-1; OSA: Obstructive Sleep Apnea; GERD: Gastroesophageal Reflux Disease; THC: delta-9-Tetrahydrocannabinol; CB1: Cannabinoid receptor type 1

Introduction

Fibromyalgia (FM) is a common condition characterized by chronic diffuse musculoskeletal pain. FM patients can suffer from a wide range of symptoms, including physical exhaustion, depression or mood disorders, stiffness and cognitive difficulties. Its pathogenesis is poorly understood, but an impairment in pain processing by both central and peripheral nervous system has been suggested to have a pivotal role [1]. FM represents a major public health issue, with an esteemed prevalence of 0.2- 6.6% [2] and a substantial associated socioeconomic burden [3,4].

A large percentage of FM patients complain about sleep disturbances, particularly difficulties in falling or staying asleep,

early morning awakenings and non-restorative sleep. A 1998 study showed that 75-90% of FM patients reported non restorative sleep [5], while sleep disturbances were reported by 94.7% of subjects in a 2008 prospective study on almost 500 FM patients [6]. Frequent awakenings at night, dissatisfaction with sleep and difficulties falling asleep are the most frequently reported symptoms [7]. In 2009, fatigue and sleep disturbance were recognized by the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials, then renamed Outcome Measures in Rheumatology) as key elements needing to be assessed in all clinical trials of FM [8]; accordingly, in 2010 non-restorative sleep was included in the Preliminary Diagnostic Criteria for Fibromyalgia by the American College of Rheumatology (ACR) [9]. A further acknowledgment of the centrality of sleep in FM pathophysiology was the inclusion of feeling unrefreshed upon waking as a key symptom in the Sufficiently high Symptom Severity scale (SSS) score [10].

The aim of this review is to summarize current evidence regarding correlations of sleep disturbances with other symptoms, particularly pain, in FM, and the pathophysiological basis of this relationship. In February 2020, we searched the PubMed/Medline, Cochrane library and Enbase/Medline databases for studies regarding this matter. We particularly focused on currently available data regarding pharmacological and non-pharmacological interventions capable of improving sleep and sleep-related quality of life in FM. However, the information is not the report of meta-analysis research and should not be considered as such.

Sleep Physiology

Sleep physiology is best studied by means of polysomnography (PSG), which includes assessment of brain activity through electroencephalography (EEG), skeletal muscle tone through electromyography (EMG) and eye movements through electrooculography (EOG). According to PSG, sleep is divided into two main stages, namely rapid eye movement (REM) sleep and non-REM sleep. REM sleep is thought to be involved in synaptic plasticity, memory consolidation and problem solving, and is characterized by desynchronized (low-voltage and mixed-frequency) waves, as well as theta activity (with frequency of 3-7 Hz), "sawtooth" waves and slow alpha waves (8-13 Hz), with concurrent skeletal muscle atony (with the exception of breathing muscles) and bursts of rapid eye movement. This is the stage associated with dreaming. On the other hand, non-REM sleep is classified in three stages: N1 (light sleep), mainly characterized by theta waves; N2 (intermediate sleep), characterized by sleep spindles and K complexes; N3 (deep sleep or slow wave sleep, SWS), characterized by slow delta waves (0.5-2 Hz) [11]. SWS physiologically represents around 20% of total sleep duration and is considered essential in granting physical and mental restoration and preserving physiological functions, including heart rate, blood pressure and regulation of many neuroendocrine paths [12].

Alterations of Sleep Physiology in Fibromyalgia

There is a well-known correlation between chronic pain and sleep disturbance. Patients with chronic pain mostly have reduction in SWS, due to micro arousals and sleep fragmentation [13,14]. In fact, pain worsens sleep quality by delaying the onset and increasing fragmentation of sleep [5]. On the other hand, deprivation of REM sleep and, more so, SWS can increase perception of pain, while increasing SWS duration can exert significant analgesic effect [15]. Disruption of REM sleep and SWS, as well as delayed sleep onset and poorer sleep efficiency, have been observed in many studies involving polysomnography conducted on FM patients [13,16-19], and their key role in reducing pain tolerance has been confirmed by several experimental studies [20,21].

There is evidence that in FM more serious sleep disorders are correlated with worsened pain perception and that patients report increased pain after more difficult nights [6,22]; inherently, sleep deprivation has been shown to reduce pain threshold, while undisturbed sleep brings pain threshold back to the baseline [23]. FM patients affected by increased daytime somnolence have been found to have higher number of tender points and to report increased pain and fatigue [16,24].

Another common EEG anomaly in FM patients is intrusion of alpha activity in non-REM stages [13,14,25,26], which has also been found in patients with chronic fatigue syndrome, as well as in several other diseases characterized by unrefreshing sleep [27]. Alpha waves intrusion in non-REM sleep is usually interpreted as marker of arousals or disturbed sleep [28]; however, its exact meaning is not fully understood, as its effect on maintaining or disrupting sleep may be dependent on the specific cerebral areas involved [25].

A study published in 1999 also found increased incidence of periodic breathing in patients with FM, which could contribute to poor sleep complained by the patients [16]; a subsequent study evidenced a high frequency of Cyclic Alternating Pattern (CAP), and particularly CAP phases A2 and A3, which are a periodic EEG sleep marker that can suggest sleep instability or poor sleep quality [30] (Figures 1 and 2). Finally, some studies showed reduced sleep spindles in N2 stage compared to healthy controls [31,32].

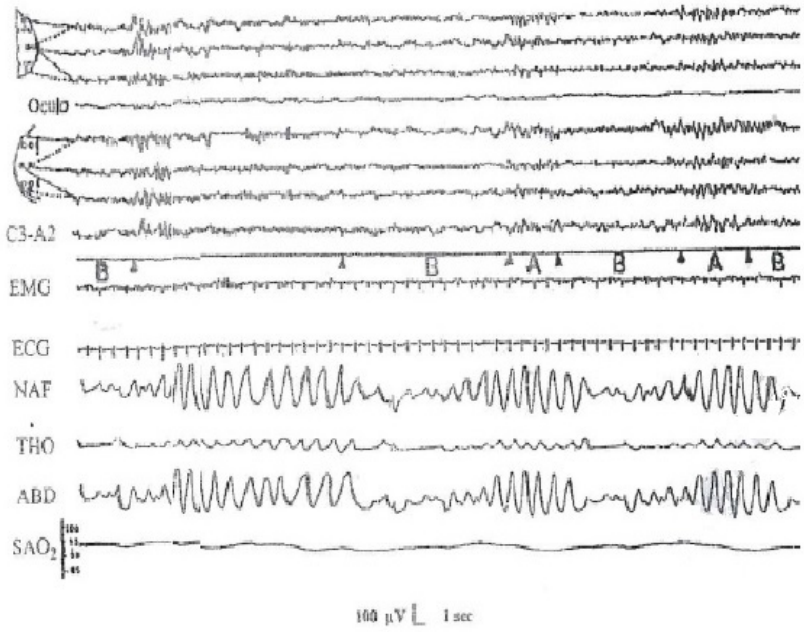

Figure 1: Periodic breathing and the Cyclic Alternating Pattern (CAP) in a patient with fibromyalgia; A and B correspond to Phase A and Phase B of CAP cycles. Oculo: electrooculogram; EMG: Submental Electromyogram; ECG: Electrocardiogram; NAF: Naso-Oral Airflow; THO: thoracic Effort; ABD: Respiratory Abdominal Effort; SAO_2: percentage of Oxygen Saturation.

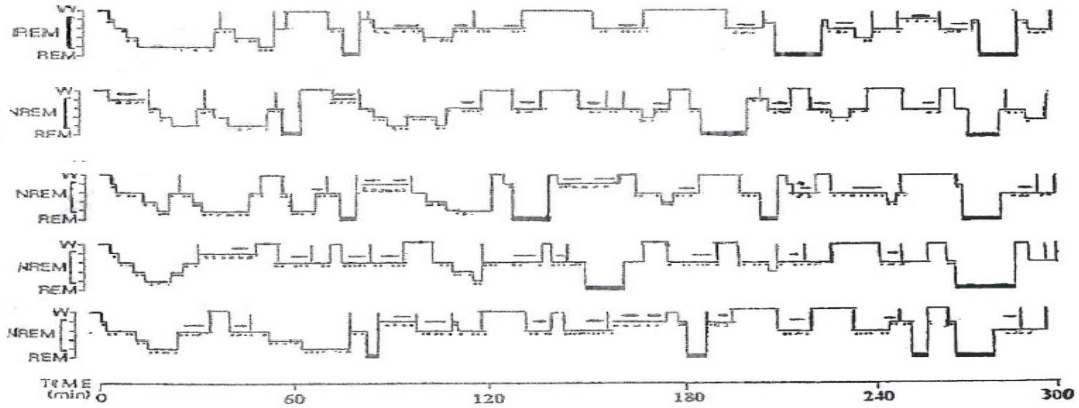

Figure 2: Sleep histograms of 5 patients with FM. The black dots correspond to sequences of the cyclic alternating pattern; black lines correspond to the periodic breathing sequences. REM: Rapid Eye Movement; NREM: Non-Rapid Eye Movement; W: Wake.

Another sleep disturbance correlated with FM are Periodic Limb Movements (PLM) [33-35], which are defined as repetitive cramping or jerking of the legs induced by an urge to move them during sleep. The high incidence of PLM syndrome in FM is probably related to increased nociceptive input [36]. CAP has been frequently observed in FM patients with PLM and these two conditions [37].

Mechanisms Underlying Sleep Difficulties in Fibromyalgia

Neurotransmission anomalies, altered circadian rhythms, alterations in endocrine homeostasis, mood disorders and impaired response to stress concur in FM pathogenesis and can explain the wide heterogeneity of FM phenotypes [38]; sleep disorders share a complex biunivocal relation to all of these aspects of the syndrome. Physiopathology of FM and sleep disturbances has been investigated in both humans and in animal models [39].

A common feature in FM is pain elicited even by light pressure exerted on so-called tender points (allodinia), as well as increased nociceptive perception evoked by harmful stimuli (hyperalgesia) [40]. These phenomena have been explained as manifestations of central nervous system (CNS) hypersensitization, which may be defined as increased brain activation in response to sensitive stimulation. In fact, physical manifestations of FM are very similar to those found in patients affected by chronic neuropathic pain [41]. Studies employing functional magnetic resonance (fMRI) found that painful stimulation on FM patients lead to activation of the same pathways involved in pain processing in normal subjects, but brain responses in FM patients were evoked by much lesser stimuli than those needed to elicit pain in normal controls [42].

Hypersensitization is usually interpreted as a maladaptive response to peripheral lesions, which leads to excessive CNS reactivity to sensitive stimuli and to persistence of pain even after the end of the stimulation [43]. Its pathogenesis is probably related to anomalies in the spinal ascending pain pathways, including excessive excitatory stimulation by neurotransmitters such as glutamate, substance P and nerve growth factor [38]. In addition, dysregulation of both serotoninergic and noradrenergic spinal descending inhibitory pathways is probably implicated in processes of central sensitization in FM; decreased levels of both 5-HT and norepinephrine have been found in spinal fluid of FM patients [44]. It has already been discussed how SWS deprivation has been associated with both central sensitization to pain and worsening of perceived musculoskeletal disturbs [15,20,27].

Moreover, decreased serotonin levels are associated with insomnia and increased sensitivity to pain in both animals and humans [45]. Reduced serotoninergic stimulation is also correlated with higher levels of substance P (SP) [46]. SP is a polypeptide acting as neurotransmitter and neuromodulator, which is involved in many physiological processes, including pain transmission and sensitization [47], mood regulation, memory, anxiety and sleep [48]. Increased levels of SP have been detected in cerebrospinal fluid of FM patients [38]. Intracerebral ventricular administration of SP in mice was found to increase sleep latency and awakenings [49]; therefore, it could be argued that raised levels of SP in FM patients could contribute to both sleep disturbances and pain.

Along with alterations of sensitive pathways, FM is also characterized by functional alteration of the autonomic nervous system (ANS) [50]. More precisely, in patients with FM both persistent ANS hyperactivation and reduced stress responses have been observed; this may be explained by downregulation of beta-adrenergic receptors following continuous over-stimulation [51]. In fact, FM patients have markers of increased sympathetic cardiovascular activity, including higher heart rate (HR), higher low frequency/high frequency ratio (which provides an index for evaluating sympathetic and parasympathetic interactions with sinoatrial node) [52] and reduced high frequency component of RR variability (HFRR) [53], but also excessive rate of syncope during tilting test [54]. As a whole, these findings suggest an overall increase in sympathetic cardiovascular stimulation at rest and an impairment in sympathetic responses in tilting test. Sleep disturbances in FM patients may significantly contribute to dysregulation of autonomic control on neurovegetative homeostasis, due to the well-known relationship between markers of sympathetic activation and both CAP [54] and spontaneous periodic breathing [55]. On the other hand, the baroreceptor system is involved in modulating ascending pain inhibition pathways, thus explaining the correlation between reduced baroreflex function and increased nociceptive sensitivity in FM [56]. Correlations between sleep disturbances (including CAP and PB) and pain in FM can thus be described as a vicious circle, in which painful exacerbations drive increased sympathetic activation and reduced sleep quality, which, in turn, cause a worsening in the patients' symptoms (Figure 3).

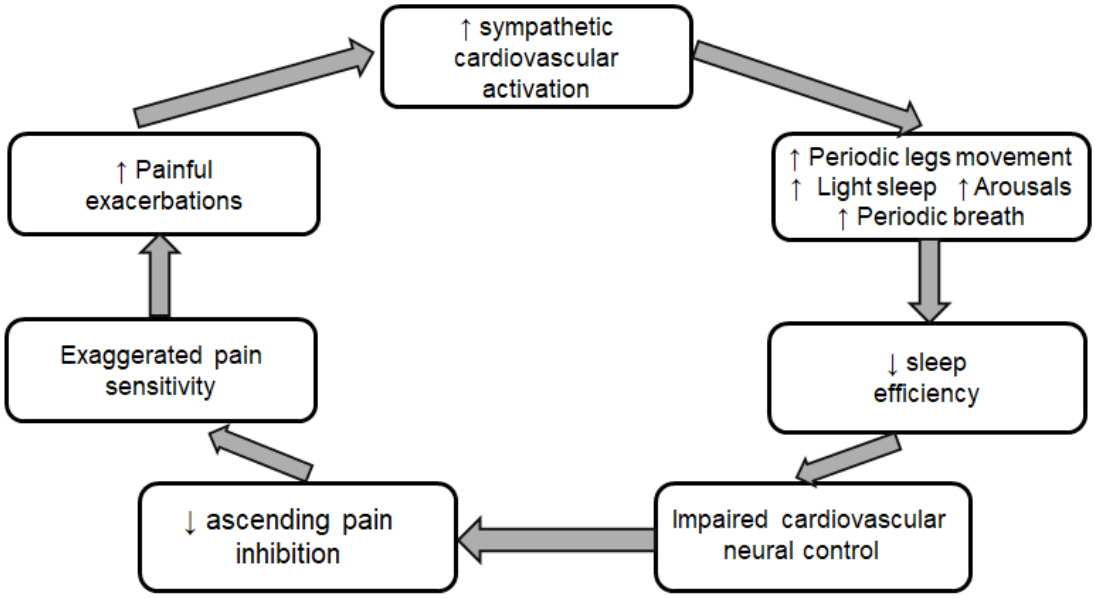

Figure 3: Vicious circle of sleep disturbances, impaired neurological and sympathetic pathways and pain sensitization in fibromyalgia.

Altered body circadian rhythms are known to affect pain perception and fatigue in FM [57]. A key role in circadian rhythm control is played by hypothalamus; in fact, dysregulation of many endocrinal axis has been reported in FM and has been investigated as probably involved in the pathogenesis its complex and multiform array of symptoms. First of all, alterations of hypothalamic-hypophysial-adrenocortical axis have been observed in FM patients [58-60], probably due to an impairment in the hypothalamic or CNS response to stressing stimuli [61]. Hypocortisolemia in FM is not associated with structural anomalies of endocrine glands, so it is probably a functional defect rather than an anatomical one; it has also been suggested that reduced hormone responses to stressors may represent an adaptive response to chronic pain [62]. Another common endocrine anomaly in these patients are decreased blood levels of growth hormone (GH) [63,64] and insulin-like growth factor-1 (IGF-1), also called somatomedin [65-67]. Nearly 70% of GH production occurs during sleep, particularly SWS. Coherently, it has been observed that reduced GH and IGF-1 production is associated with sleep fragmentation and alpha-wave intrusion during deep sleep [68,69], while not being associated with obstructive sleep apnea (OSA) in FM [70]. GH and IGF-1 are involved in muscle repair after microtraumas and in transmission of sensory stimuli from damaged muscles, therefore their downregulation could play a central role in pathogenesis of FM. This hypothesis was corroborated by interventional, randomized studies finding that GH replacement therapy significantly reduced pain perception and the number of tender points in FM patients [71-73]. An additional anomaly found in FM patients are increased levels of plasmatic melatonin, which have been interpreted as a possible marker of greater vulnerability of the hypothalamic-hypophysis axis to functional alterations induced by physical or mental stress [74].

Finally, FM patients are often affected by mood disorders, which are known to have bidirectional relationship with sleep disturbances [75]. In fact, poor sleep quality is a risk factor for developing psychological disorders [76]; on the other hand, insomnia and other sleep disturbances are a key feature of many psychiatric diseases, including anxiety [77] and depression [78]. Additionally, a 2014 study found that patients with concurrent FM and depressive disorders were affected by worsened physical and mental symptoms compared to FM controls [79]. Therefore, it could be argued that sleep disturbances in FM can both enhance and be enhanced by mood disorders [80].

Treatment of Sleep Disturbances in Fibromyalgia

Assessment and treatment of sleep disturbances in FM is of primary importance, due to their high frequency, their serious impact on the quality of life and their close correlation with the other main symptoms of the syndrome (namely musculoskeletal pain, affective disorders and exhaustion). FM symptoms are often difficult to be treated effectively, with scarce response to conventional analgesic and hypnotic drugs, hence the necessity of a multidisciplinary approach combining both pharmacological and non-pharmacological (physical, cognitive, environmental and educational) interventions [81]. An appropriate strategy

would necessarily comprehend adequate evaluation of clinical history, including comorbidities, sleep habits and lifestyle [81,82]. Specifically, it is recommended to rule out comorbidities which can worsen sleep-related symptoms, such as OSA, congestive heart failure, restless legs syndrome or Gastroesophageal Reflux Disease (GERD), and to investigate environmental conditions during sleep (e.g. noise, snoring partners, troublesome light sources). Promotion of good sleep hygiene practice can prove useful; for example, it should be suggested to reduce assumption of stimulants (such as caffeine, theine, nicotine or other drugs) or alcohol before bedtime, as well as to sleep an appropriate number of hours, to maintain regular sleep-waking rhythms (even at weekends) and to avoid demanding or stressful activities before rest [83].

Availability of safe effective pharmacological treatment for FM is still, at least partially, an unmet need. There are currently 3 drugs approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for this purpose: the anticonvulsant pregabalin and two serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine and milnacipran. All these medications have demonstrated to exert a beneficial effect on sleep [84-86], even if they are not specifically approved for treatment of FM-related sleep disorders.

SNRIs can significantly improve fatigue, pain and mood disorders, but scarce data exist regarding effectiveness in improving sleep quality or sleep organization [87,88], suggesting that their beneficial action on sleep is mostly consequent to their analgesic effect [85].

On the other hand, pregabalin seems more effective than SNRIs in enhancing sleep [89]; this may be explained by recent findings that pregabalin does improve sleep quality and sleep structure. In fact, a 2015 randomized controlled trial found that patients treated with pregabalin had decreased number of wake/sleep bouts and increased sleep bout duration, with significant correlation with increased SWS [90]. Also gabapentin, a chemically related anticonvulsant, have proved to increase sleep quantity and quality [91].

The tricyclic antidepressant amitriptyline is also frequently employed to treat pain and sleep disturbances in FM, with records of good results in clinical practice; anyway, experimental data regarding its effectiveness are still lacking [92,93]. A recent Cochrane review found no studies regarding effectiveness of amitriptyline in treatment of sleep disturbances [94].

Other commonly prescribed medications for dealing with sleep disturbances in FM are benzodiazepines and so-called nonbenzodiazepine Z-drugs, such as zolpidem and zopiclone. However, these drugs have very limited effect on sleep structure and have been found to be scarcely effective in FM [95,96].

Sodium oxybate is a prodrug which is metabolized to gamma-hydroxybutyrate and is effective in improving sleep architecture, while it has no direct analgesic effect. Despite that, several clinical trials show that sodium oxybate is also able to reduce pain in FM patients, thus reinforcing the assessment that sleep improvement is a key strategy for pain control in FM [97]. However, sodium oxybate is currently approved by FDA and EMA only for treating cataplexy and narcolepsy [98,99]. Inherently, also melatonin, a commonly prescribed drug for insomnia and jet lag, has been shown to reduce pain by modulating central nervous system inhibitory descendent pathways in FM patients, particularly when combined with amitriptyline [100]. Finally, clinical trials have found the myorelaxant cyclobenzaprine to be able to exert favorable effects on sleep quantity and quality in FM patients [101-103]. On the contrary, a recent study has pointed out that opioid medications negatively alter sleep architecture in FM patients, prompting greater sleep onset latency, greater duration of light sleep stages and shorter duration of SWS; these effects seemed to be enhanced in elderly patients and by higher drug doses [104]. It has been advocated that poor therapeutic response to opioids in FM is due to reduced μ-opioid receptors found in several areas of the brain, compared with healthy individuals [105,106].

Cannabinoids could prove another valuable tool for treating FM-related pain and sleep disturbance. A 2010 study found that nabilone, a synthetic drug with similar action to delta-9-tetrahydrocannabinol (THC), was superior to amitriptyline in improving sleep quality in FM patients, but had no effect on pain or mood disorders; reported adverse events were similar to amitriptyline [107]. Many studies found that cannabinoids can improve sleep quality in patients affected by chronic pain [108]; limited evidence also suggests that THC can increase the amount of SWS [109]. This effect is probably due to modulation of sleep by presynaptic cannabinoid receptor type 1 (CB1) in cholinergic pathways in brainstem and basal forebrain, which are involved in sleep initiation and maintaining [110]. However, further data are needed in order to explore if cannabinoids could be a valid and safe therapy for treating FM.

Ultimately, due to scarcity of available data and to high clinical heterogeneity of FM, both pharmacological and nonpharmacological treatments should be tailored to patients, considering socioeconomic status, current and previous diseases and potential drugs' side effects and interactions with other therapies [82].

Conclusion

Sleep disturbances have been established as a main feature in the complex array of symptoms in FM, with great impact on health-related quality of life. They are closely correlated with other symptoms commonly reported by FM patients, including

pain and fatigue, due to both common etiopathogenesis and to mutual interference of pathophysiological manifestations of this condition. It has also been established that correction of sleep disturbances may prove very beneficial in obtaining an overall improvement in symptoms and quality of life in FM[5].

Along with treatment with currently available drugs, an all-round assessment of patients' clinical history and comorbidities, together with factors (e.g. habits and drugs) interfering with sleep hygiene, should be recommended. In fact, evaluation of sleep should always be included in FM management, including studying sleep architecture by means of polysomnography.

Moreover, while many studies have been conducted regarding sleep disturbances in FM patients, insufficient data from clinical trials are available about effectiveness of pharmacological and nonpharmacological interventions in correcting such pathophysiological anomalies and their impact on quality of life. Lack of reliable information inevitably impairs physicians' availability of effective treatment options. Therefore, non-pharmacological therapies aimed at improving sleep hygiene can still be currently considered the first line treatment for sleep-related symptoms in FM. Further studies are thus needed to evaluate possible remedies for improving sleep quality in FM patients.

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