Deciphering the Role of Sleep in Fibromyalgia Syndrome

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Abstract

Fibromyalgia syndromes (FMS) is a chronic and debilitating musculoskeletal pain disorder of unknown aetiology with usual accompanying features of fatigue, sleep disturbances and stiffness and is one of the least understood pain syndrome in medicine today. Other symptoms include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching and chronic sleep disturbances. In addition to this FMS is perceived as a disorder of central sensitization. Polysomnography data has demonstrated that FMS patients have reduced short-wave sleep suggestive of wakefulness during non-REM (rapid eye movement) sleep. In FMS, the combination of pain and sleep disturbance is a double-edged sword: the pain makes sleep more difficult and sleep deprivation exacerbates pain and the reduction in sleep disturbance is usually followed by improvement in pain symptoms. Sleep disturbances are among the most common symptoms of FMS, a chronic condition affecting the spinal cord and brain that causes patient to feel pain and fatigue, and affects concentration. In fact, along with the tiredness, pain, and psychosocial distress, sleep disturbances are a core feature in FMS patient. In the last few years, it has become increasingly clear that treating the associated sleep disturbance improves the daytime symptoms of FMS. Mechanistically, sleep deprivation impairs descending pain-inhibition pathways that are important in controlling and coping with pain. Clinical trials of pharmacological and non-pharmacological therapies have shown that improving sleep quality can reduce pain and fatigue, further supporting the hypothesis that sleep dysfunction is a pathogenic stimulus of FMS. Therefore, it is important to understand the sleep disturbances in FMS patients. In this review we will try to elucidate the sleep abnormalities in FMS patients.

INTRODUCTION

FMS is a chronic musculoskeletal pain disorder of unknown aetiology, characterised by chronic widespread pain and muscle tenderness and the presence of tender points on examination. Patients experience both allodynia (pain from a normally non-painful stimulus) and hyperalgesia (inappropriately intense pain from a normally painful stimulus). Other common accompanying features are fatigue, sleep disturbances, stiffness, and paraesthesias, headaches, Raynaud’s like symptoms, depression and anxiety [1]. FMS is much more than widespread pain as it overlaps substantially with other central sensitivity syndromes such as chronic fatigue syndrome, irritable bowel syndrome, chronic pelvic pain syndrome/primary dysmenorrhoea; temporomandibular joint pain, multiple chemical sensitivity, restless legs syndrome and interstitial cystitis. The diagnostic criteria have changed repeatedly, and there is neither a definitive pathogenesis nor reliable diagnostic or prognostic biomarkers. Clinical and laboratory studies have provided evidence of altered central pain pathways. Few patients with FMS also report difficulty with swallowing, bowel and bladder abnormalities, numbness, tingling and cognitive dysfunction [2]. FMS is a persistent and potentially debilitating disorder that can have a devastating effect on quality of life, impairing the patient's ability to work and participate in everyday activities, as well as affecting relationships with family, friends, and employers. It imposes heavy economic burdens on society as well as on the patient [3].

There is as yet no cure for FMS. Some treatments have been shown by controlled clinical trials to effectively reduce symptoms, including medications, behavioral interventions, patient education, and exercise. FMS is one of the least understood pain syndrome in medicine today, which is a chronic disorder characterized by persistent and widespread pain, with an estimated prevalence of 2-4% in the adult general population [3.4% for women and 0.5% for men] [4]. FMS definition and content has changed repeatedly in the 110 years of its existence. The most important change was the requirement for multiple tender points and extensive pain for diagnosis of this condition that arose in the 1980s (1990 American College of Rheumatology classification criteria) [5]. In 2010, a second shift revised the definition of FMS, so it came into being in the form of the preliminary 2010 ACR criteria that excluded tender points,....
allowed less extensive pain, and given importance to patient-reported somatic symptoms and cognitive difficulties [6].

Medical researchers have tried to clarify the association between sleep disturbances and pain. Very little is known but a few key findings indicate that sleep and pain are intricately linked.

For example, studies of patients experiencing pain after surgery show disturbed sleep, reduced rapid eye movement (REM) sleep, and a normalization of sleep as recovery proceeds. People with FMS may also experience an alteration in their patterns of slow wave sleep, which is the deepest stage of sleep. FMS patients consistently complain of poor sleep quality, exhibiting insomnia symptoms, and feelings of disturbed sleep, daytime tiredness, and sleepiness [7,8]. However, some researchers [9] still claim that those sleep complaints would reflect some kind of sleep misperception in FMS. Although extensive research has focused on sleep in FMS patients since the mid-1970s, little is known about the contribution of polysomnographic (PSG) parameters determining subjective sleep quality in FMS. In their pioneering PSG studies, Moldofsky and colleagues [10,11] were the first to describe specific α-electroencephalographic (EEG) sleep patterns in FMS patients. Subsequent studies suggested that α-EEG sleep would explain unrefreshing sleep in FMS [12,13]. Unfortunately, most of the research investigating PSG parameters in FMS patients compared to controls has been inconclusive [14]. Therefore, in this review, we will try to elucidate the relationship between sleep and FMS.

**What is sleep architecture?**

Sleep architecture describes the structure and pattern of sleep and encompasses several variables. Sleep quotas refer to the amount of time spent in REM and NREM sleep. Sleep duration is the total time spent asleep in a 24-hour period. The duration of a NREM-REM cycle [from the beginning of NREM to the end of REM] is also an important aspect of sleep architecture. Phasing of sleep describes how sleep is distributed across a daily cycle: polyphasic sleep consists of multiple bouts of sleep in a 24-hour period, while monophasic sleep consists of a single bout of sleep in a 24-hour period. Sleep architecture varies widely, and is thought to be significantly influenced by genetics. [15] The evolution of different types of sleep architecture is influenced by a number of selective pressures, including body size, relative metabolic rate, predation, type and location of food sources, and immune function. The importance of sleep research is both in medicine and in theoretical area. However, there are many sleep disorders, e.g., the most frequent are insomnia, narcolepsy, sleep apnoea; many other disorders manifest themselves through sleep disturbances [e.g. depression, schizophrenia, chronic fatigue syndrome, fibromyalgia syndrome etc] [16]. Sleep has been postulated to be important for the consolidation of memory and for regeneration of the body and brain. It is believed to maintain homeostasis and optimizing multiple physiologic functions, including psychiatric, neurologic, cardiovascular, endocrine, and immunologic functions [17-19]. After the pain, sleep disturbances are the second most frequent indicator of illness. Sleep is not a quiescent state. Two processes govern sleep: the first, the homeostatic process, is often referred to as the “sleep drive,” and, the second, the circadian system, refers to the 24-h sleep-wake cycle and governs many physiological processes including production of hormones (e.g., melatonin), gene expression, and body temperature. Sleep and wake cycles are controlled by the pacemaker activity of the suprachiasmatic nucleus in the hypothalamic region of the brain but can be disrupted by diseases of the nervous system causing disordered sleep. The high level of brain activity can be detected on an electroencephalogram (EEG). Sleep spindles along with K-complexes are defining characteristics of, and indicate the onset of, stage 2 sleep. Slow wave sleep (SWS), which may be referred to as deep sleep, occurs in Stage 3 NREM and is characterized by synchronized EEG activity. The fourth stage is characterized by rapid eye movements [REM] sleep, which can be detected by a decrease in muscle activity.

**Stages of Sleep**

Polysomnography records muscle tone, and eye movements and measures electrical activity of the brain using the electroencephalogram (EEG). From such observations, sleep is conventionally divided into:

- **NREM-Stage 1** is the beginning of the sleep cycle. It is light sleep where you drift in and out of sleep and can be awakened easily. In this stage, the eyes move slowly and muscle activity slows. This period of sleep lasts only a brief time (around 5-10 minutes).

- **NREM-Stage 2** is the second stage of sleep and lasts for approximately 20 minutes. Eye movement stops and brain waves become slower with only an occasional burst of rapid brain waves.

- **NREM-Stage 3** is referred to as deep sleep or delta sleep. It is during these deepest levels of sleep that the body restores and refreshes itself.

- **REM (Rapid Eye Movement)** is when dreaming occurs. REM sleep is characterized by eye movement, increased respiration rate and increased brain activity.

The sleep stages normally occur in an orderly sequence of 4 sleep cycles of approximately 90 minutes, each ending with a period of REM sleep. As the night progresses, the proportion of sleep occupied by the REM phase increases and SWS decreases. Thus, SWS is prominent in the early part of the night but is usually not present beyond the second sleep cycle. The timing and duration of sleep depend largely on an endogenous circadian rhythm, but there are additional homeostatic mechanisms that act to compensate for any sleep deficiency by increasing the amount of slow wave sleep. For example, when subjects are deprived of sleep during the first third of the night, there is subsequent compression of the sleep cycle with a rapid progression to stage 4 sleep. Together with a shortened REM latency, this results in a markedly increased proportion of total sleep time spent in SWS [20]. Although the function of these sleep changes remains to be fully elucidated, it is clear that, in young healthy subjects, short-term sleep deprivation, or selective deprivation of slow-wave sleep, results in a profound decrement of cognitive function, irritability, and increased sensitivity to pain [21]. Interestingly, these are the symptoms commonly reported by patients with FMS. Patients with FMS lack the deep, restorative level of non-REM sleep. Consequently, patients with FMS often wake up in
the morning without feeling fully rested. Some patients with FMS wake up with muscle aches or a sensation of muscle fatigue as if they had been exercising all night.

Non restorative sleep (NRS)

From ancient times, sleep has been valued as a restorative time, making the person feel energized and refreshed. Modern science has shown this isn’t just a subjective feeling. During sleep the immune system and the cardiovascular system experience a reprieve which could be called a restoration, and other organ systems are restored. The concept of non restorative sleep (NRS) is based on the restorative theory, which considers brain activity during sleep as essential for the restoration of body and mind functioning. NRS usually refers to a subjective feeling of being un refreshed after sleep or having poor-quality sleep [22]. In the context of primary insomnia, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV defines NRS as “self-reported restless, light or poor quality sleep.” Abnormal sleep restoration results in feelings of tiredness, sluggishness, or fatigue, which are often associated with NRS. Thus, NRS has been linked to waking up feeling un refreshed. NRS is common among many patients with sleep disorders, including apnea, and has been considered a primary symptom of insomnia. However, NRS is often not a primary, but rather a secondary, symptom of insomnia, and is associated with poor health or negative mood. However, definitions of NRS seem to differ in the literature and the DSM-IV-TR definition does not always agree with the definition of NRS in studies of FMS, in which participants may be labeled as having NRS based on symptoms of feeling un refreshed after sleep of seemingly adequate latency, maintenance, and duration [23]. Although many studies have focused on symptoms of insomnia associated with these chronic pain syndromes. One reason for the small number of studies on NRS is lack of a uniform definition, known pathogenesis, validated assessment, and treatment strategies for the condition. Thus, more studies are warranted in order to better understand this unique disorder, which could provide important clues to the causes of FMS and to the overall function of sleep.

Causes of Non restorative Sleep

There are many causes of insomnia and NRS. These include learned behavioral patterns that make sleep onset difficult, such as exercising or watching television before bedtime. Insomnia and NRS can also be caused by mood disorders (eg, depression, anxiety); medical disorders (eg, diabetes, cardiopulmonary disorders, pain disorders of various types); neurologic disorders (eg, Parkinson disease, seizure disorder, dementia); primary sleep disorders, such as obstructive sleep apnea syndrome and restless legs syndrome; and chronic pain syndromes, such as fibromyalgia. Medications such as decongestants, dietary intake of caffeine and substance misuse/abuse (eg, alcohol or stimulants) can also lead to insomnia and NRS [24].

Both insomnia and NRS have been associated with increased rates of medical and psychiatric comorbidities, as well as with increased rates of mortality, although the exact causative relationship between disturbed sleep and these conditions is unknown [25].

Sleep Abnormalities in FMS

Insomnia and feeling unrefreshed upon awakening are common concerns among patients with FMS. Compared with healthy controls, most patients with FMS perceive their sleep to be of poor quality almost always reporting it as non restorative. More specifically, NRS is one of the major complaints among patients with FMS. Whenever, sleep is perceived as restful, patients with FMS report substantial improvement in their daytime symptoms. Additionally, factors such as inadequate pain control or poor sleep and lifestyle habits may exacerbate FMS. Thus, a careful evaluation, including a detailed sleep history, is essential, and further investigations may be required to rule out any other disorders. Patients with FMS often describe feeling as if they “have not slept at all,” and it can be difficult to determine the exact relationship between sleep and pain in patients with FMS. For example, sleep deprivation may potentially contribute to the generation of symptoms of FMS and certain primary sleep disorders are known to be particularly associated with FMS. Obstructive sleep apnea is a common condition, particularly in men, in which sleep is repeatedly interrupted by obstruction of the upper airway with hypoxia, resulting in symptoms of insomnia and fatigue. In addition to this FMS patients have lower melatonin secretion during the hours of darkness than the healthy subjects. This may contribute to impaired sleep at night, fatigue during the day and changed pain perception [26].

Another primary sleep disorder is the syndrome of restless leg syndrome or periodic limb movements, where episodic repeated involuntary brief movements of the legs occur, causing fragmentation of sleep. This condition, which occurs frequently in older individuals, needs to be considered in patients with FMS who describe restless sleep. A large percentage of patients with FMS reports sleep disturbances, including difficulty falling asleep, difficulty staying asleep, early morning awakening, and NRS [27,28]. Additionally, a variety of physiologic abnormalities of sleep have been documented in patients with FMS. PSG findings in patients with FMS include the intrusion of alpha waves, which are typical of a wake states, into non-REM sleep. These alpha-intrusions correlate with overnight pain reporting, and some investigators have proposed that they may be indicators of NRS [29]. However, alpha-intrusions are not specific to FMS, and may occur in a variety of other conditions, and may also be seen in normal individuals [30]. Patients with FMS have also been shown to have increased arousals from deep sleep, decreased time spent in slow-wave sleep, and decreased time spent in REM sleep [31]. Some have raised the possibility that these sleep abnormalities may contribute to increased pain perception in patients with FMS.

Guymer et al [32] showed that fatigue levels were significantly influenced by age and sleep disturbances, and sleep disturbances were significantly predicted by fatigue. In two studies, more than 90% of FMS patients reported disturbed and non restorative sleep [34]. In addition, FMS patients have reported difficulties falling or staying asleep, non restorative sleep, and waking up early in the morning [22]. According to Moldofsky, [22] nonrestorative sleep is not the same as insomnia, as it is essentially a qualitative phenomenon. Restorative or refreshing sleep depends on the amount, one sleeps and when, one sleeps. People who experience

non restorative sleep characterize their sleep as light or superficial [22]. According to the American College of Rheumatology [ACR], three core symptoms of non restorative sleep should be used when diagnosing FMS: waking up feeling unrefreshed; cognitive difficulties; and fatigue [5] Sleep duration and nightly wake time did not, according to Anderson et al, [35] predict clinical FMS pain, although Schaefer et al [34] showed that sleep disturbance measured by Medical Outcomes Study Sleep Scale, increased significantly in severe FMS. Furthermore, Roizenblatt et al [36] described that compared with healthy controls, most patients with FMS perceived their sleep to be of poor quality, reporting it as non restorative, and reported worsening pain symptoms after non restorative sleep. Bigatti et al [37] found that FMS patients exhibited persistent poor sleep quality, for instance, sleep duration and sleep latency that eventually leads to increased pain, disability, and depression. A causal relationship and interaction may exist between FMS, sleep, and mood disorders. Sleep disturbances can affect a patient’s health-related quality of life (HRQoL); a comparison between matched controls and persons with FMS showed a statistically significant difference between sleep difficulty symptoms, such as initiating and maintaining sleep, and HRQoL. Consequences of the sleep difficulty symptoms such as social isolation and decreased physical activity were shown to severely impact HRQoL and, further, the effect extended beyond HRQoL. The impact of sleep abnormalities was also shown in an interview study investigating general quality of life of working women with FMS. The women highlighted the importance of having social relations, being active, and participating in society as essential for experiencing general quality of life [38].

The sleep abnormalities described in FMS seem to be similar to those of other forms of insomnia, raising the intriguing possibility that improvement in sleep may be one of the mechanisms by which medications improve pain symptoms in FMS. However, patients with FMS do not typically have global improvement in response to therapies, such as benzodiazepines, that are often effective for other forms of insomnia [39]. Also, napping may not always reduce fatigue in patients with FMS [40]. Affleck et al [41]. Examined subjective sleep quality, pain, and attention to pain in 50 women with FMS. They produced data that support the hypothesis that “sleep difficulties precede, rather than follow, increased pain during the day” and the best predictor of pain levels is non restorative sleep the night before [42]. Moldofsky has shown that the alpha-delta activity in patients with FMS is related to pain, energy, and mood and that the amount of alpha frequency during sleep correlates with an increase in overnight pain measures. [21] On the other hand, in a study of healthy volunteers, Drewes et al [43] demonstrated that deep pain, particularly muscle pain, causes an arousal effect during sleep and that this results in a decrease in SWS and increase in alpha activities. Alpha sleep correlates with perceived shallow sleep and a predisposition to arousal leading to fragmented sleep [44]. Although the cause-effect relationship between pain and sleep in FMS is complex, it is clear that the promotion of restful sleep is an important priority in the treatment of FMS.

The Relationship between FMS and disturbed sleep

Sleep disturbances are presumed to result from the pathophysiolologic changes that occur with FMS, various researchers have raised the possibility of a bidirectional relationship between NRS and pain in FMS [45]. Higher levels of daytime sleepiness have been shown to be correlated with an increased number of tender points in patients with FMS, although the cause of this association remains unknown. Studies of experimentally induced sleep deprivation have shown that disruption of slow-wave sleep can result in increased symptoms of pain [46] Additionally, patients with sleep disorders, including sleep apnea syndrome and restless legs syndrome, have been shown to have pain responses similar to those in patients with FMS. And, while not all studies agree, patients with FMS may have a higher prevalence of specific sleep disorders, including sleep apnea and restless legs syndromes. [47,48]. Based on these findings, the disordered sleep in FMS may be a cause of enhanced pain. Furthermore, Fatima et al [49] have demonstrated that patients with FMS exhibit alterations in circadian rhythms of serum cortisol secretion. This increase in nocturnal serum cortisol in patients group suggests dysregulated circadian patterns which may explain in part the patient complaint of unrefreshing sleep.

The relationship between FMS, mood disorders, and sleep disorders is also complicated, and the causal relationships and interactions of these syndromes have yet to be fully understood [50-52]. Current and persistent sleep problems often precede new mood disorders, and depression is known to diminish the pain threshold. Therefore, depression may be a mediator of pain and poor sleep in FMS. On the other hand, it is conceivable that FMS -related pain may lead to disturbed sleep, with the combination of pain and disturbed sleep ultimately leading to depression. It may also be true that some other abnormally leads to the pain and mood and sleep disorders seen in FMS. Some researchers believe that the neurotransmitter serotonin may be the link between these disorders. Serotonin is thought to be important in pain-signal transmission, mood, and sleep regulation, and serotonin abnormalities may play a role in FMS and related sleep and mood disorders [53]. Some studies have shown decreased serotonin levels in patients with FMS [51]. Fatima et al [54] demonstrated that there was a weak circadian pattern of serum levels of serotonin in patients with FMS. Interestingly, this decrease in serum serotonin in the patient group throughout the day is important because it may explain in part the patient’s complaint of un refreshing sleep and also is found to correlate with the level of disease severity. In addition, clinical trials using the serotonin-norepinephrine reuptake inhibitor duloxetine have shown reduced FMS-related pain and mood and sleep difficulties [55]. Further research is necessary to fully characterize the relationship between neurotransmitters, FMS, and disorders of mood and sleep.

Importance of sleep assessment in FMS patients

Sleep abnormalities are commonly reported by patients with FMS, but disturbed sleep or NRS is not among the universally accepted diagnostic criteria of FMS, which were established in 1990 by the American College of Rheumatology (ACR) [5]. However, the newly proposed 2010 ACR Preliminary Diagnostic Criteria for FMS and Measurement of Symptom Severity does include assessment of sleep disturbance as part of the classification system. In particular, these new criteria use patient-reported measures of un refreshed sleep and problems
with sleep assessed with visual analogue scales to support the
diagnosis of FMS, although as noted above, the definition of NRS
used in studies of FMS may differ from definitions used in other
conditions or studies [6].

Although primary sleep disorders and disturbed sleep may
be related to FMS symptoms, studies have yet to conclusively
demonstrate that management of identified sleep disorders and
symptoms can reduce FMS symptoms. Nevertheless, the fact
that such improvements may occur in any given patient, make
it reasonable to include evaluation of sleep and its disturbances
in the history and examination of patients with FMS [56].
Furthermore, given that the newly proposed ACR diagnostic
criteria for FMS include sleep-related factors, obtaining a sleep
history is an important factor in both the diagnosis and ongoing
assessment of FMS [6].

Principles of the evaluation of sleep and its disorders have
been described in detail elsewhere [57]. A good sleep history
in patients with sleep-related problems, in the context of any
medical condition, including FMS, contains data on self-reported
sleep, sleep patterns, and symptoms of daytime sleepiness. It
also includes assessment of potentially impaired sleep hygiene,
which can be defined as practices that interrupt normal, quality
nighttime sleep and daytime alertness, and encompasses
activities throughout the day and before bedtime that may affect
sleep [58,59]. Standardized assessments of sleep and NRS for
management of patients with FMS are not yet in widespread
use; however, visual analogue scales for self-reported sleep
symptoms from the newly proposed ACR criteria for FMS may be
a good option for use in the near future [6].

Patients with FMS and NRS should also be questioned about
other disorders that may influence sleep. These include sleep
apnea syndrome; periodic limb movement disorder; mood
disorders (eg, depression, anxiety) and medical conditions that
may be associated with sleep disorders, such as diabetes, thyroid
disorders, and hypertension [60]. Symptoms of sleep apnea
syndrome that patients and their sleep partners should be asked
about include snoring or episodes of apnea witnessed by the
sleep partner. On examination, obesity; increased neck size (>16 inches); and enlargement of the tonsils, soft palate, or tongue
may indicate increased risk for obstructive sleep apnea syndrome
[60,61]. Finally, to evaluate for limb movement disorders that
disrupt sleep, patients can be asked whether their bedcovers are
significantly disrupted or removed in the morning or if a sleep
partner reports being kicked at night [62,63].

SUMMARY

Sleep disturbances are prevalent in the general population.
Disturbed sleep is poorly understood, and variably defined.
A widely used definition of disturbed sleep includes feeling
persistently unrefreshed upon awakening, despite normal
sleep duration, and occurrence in the absence of distinct sleep
disorders. Although disturbed sleep is strongly associated with
daytime impairment, pain, fatigue, and EEG arousals in non-
REM sleep, causal links have not yet been established. Sleep
disturbances should not be conceptualized as a symptom of
insomnia, such as difficulty initiating and maintaining sleep.
Because of the lack of standardization, however, only limited
conclusions can be drawn about it. The condition has the
potential to contribute to our understanding of sleep, which is
an important goal with considerable health implications. Finally,
disturbed sleep is an important symptom among patients with
FMS, who often report widespread pain, fatigue, and cognitive
and emotional difficulties.

CONCLUSION

Disturbed sleep or NRS is a hallmark of FMS. Few studies have
been devoted to NRS in patients with FMS, mostly because of the
lack of a widely accepted definition, an unknown pathogenesis,
and no validated assessment and treatment strategies. Improved
understanding of this important, unique symptom not only
may enhance our understanding of FMS but could also result in
improved treatment outcomes. Overall, NRS plays an important
role in many chronic conditions involving fatigue, pain, cognition,
and mood, such as FMS and CFS. More research needs to be done
in order to definitively understand the relationship between NRS
and FMS. Furthermore, general sleep hygiene guidelines, such
as maintaining daily routine and avoiding caffeine close to bed
time, should be followed in order to maximize restorative sleep
in patients with FMS.

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