

REVIEW ARTICLE

Sleep-Wake Disturbances in Fibromyalgia

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Fibromyalgia characterized unrefreshing sleep, sleep physiological disturbances, depressed mood, and cognitive difficulties in addition to widespread pain, persisting for at least 3 months, and a minimum of 11 of 18 tender points, tenderness, and other somatic symptoms. Among polysomnographic abnormalities, the most common finding is the intrusion of alpha rhythm into NREM sleep (alpha-delta sleep). Patients with fibromyalgia also exhibit prolonged sleep onset latencies, an increased number of arousals, and increases in stage 1 sleep. However, alpha-delta sleep is not specific or pathognomonic for the diagnosis of fibromyalgia and may represent an epiphenomenon of an undefined central nervous system disturbance. A strong relationship between sleep disturbance and pain perception is clear in fibromyalgia. The interactions among immune system, pain, and sleep disturbance and therapeutic implications are discussed in this article. **(Sleep and Hypnosis 2002;4(3):93-105)**

Key words: *fibromyalgia, sleep disturbance, alpha-delta sleep, pain, immune system*

INTRODUCTION

According to the multicenter committee report by the American College of Rheumatology (ACR), a diagnosis of fibromyalgia must include a history of widespread pain, persisting for at least 3 months, and a minimum of 11 of 18 tender points (1). Patients with fibromyalgia also experience unrefreshing sleep, sleep physiological disturbances, depressed mood, and cognitive difficulties (2). The ACR Multicenter Committee noted the following: migraine and tension headaches; irritable bowel syndrome; dysmenorrhea and urinary frequency; paresthesias or dysesthesia; Raynaud's phenomenon; and sicca syndromes.

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A recent population-based study in the United States found that the overall prevalence of fibromyalgia was 2%. Among women the prevalence rate was 3.4%, whereas among men it was 0.5% (3).

NEUROSCIENCE AND NEUROENDOCRINOLOGY OF FIBROMYALGIA

Although genetic factors and peripheral mechanisms have suggested in etiopathogenesis of disorder, attention has been directed to the identification of central mechanisms related to neuroendocrine abnormalities and neuroimmunologic changes that distinguish patients with fibromyalgia from healthy persons. Several laboratories have reported evidence that fibromyalgia is associated with a neuroendocrine disorder characterized by abnormal function of the hypothalamic-pituitary-adrenal (HPA) axis including hyperactive ACTH release and adrenal hyporesponsiveness (4,5). Crofford et al found that patients with

fibromyalgia had significantly lower mean 24-hour urinary free-cortisol levels than healthy controls. Total and free cortisol levels in plasma collected in the evening were significantly elevated among the patients with fibromyalgia. Stressors such as a psychological or emotional disturbance, metabolic or physiologic disturbance, and infection or inflammatory changes can disturb homeostasis and the HPA axis begin to active and re-establish homeostasis.

Sleep is important in controlling the release of growth hormone (GH). GH is normally produced by pituitary during deep sleep. It was shown that patients with fibromyalgia were characterized by significantly lower levels of somatomedin C than healthy controls (6). Low levels of somatomedin C reflects a disruption of GH secretion that is influenced by blunted HPA axis responses or adrenal hyporesponsiveness (4). On the other hand, Russell has reported lower levels of DHEA sulfate in fibromyalgia patients (7).

Evidence regarding the role of neuroendocrine axis in fibromyalgia also is provided by studies of serotonin and substance P levels in patients and healthy controls. Serotonin plays a role in sleep, pain threshold, vascular constriction and dilatation. During the past decade, many studies found low serum levels of serotonin and cerebrospinal fluid (CSF) levels of serotonin metabolite, 5-hydroxyindole acetic acid (5-HIAA) in patients with fibromyalgia (8-11). It was also found that levels of tryptophan were low in serum and in CSF (11,12). In 1988, Vaeroy and his associates (13) demonstrated that patients with fibromyalgia were characterized by significantly higher CSF levels of substance P than healthy controls. Russell et al (14) replicated this finding in patients with fibromyalgia and controls. According to findings of these investigations, it may be suggested that the mean substance P levels among patients with fibromyalgia are three to four folds higher than that of the controls.

Mohammad Yunus (15) suggested that a complex interaction between central and peripheral factors was responsible the high levels

of pain and fatigue in fibromyalgia. He suggested that genetically predisposed individuals who are exposed to viral infection or other stressors display neurohormonal dysfunction such as perturbed HPA axis activity. This neurohormonal dysfunction might lead to an aberrant central pain mechanism characterized by a functional deficiency of inhibitory neurotransmitters at the spinal or supraspinal levels (e.g., serotonin) or overactivity of excitatory neurotransmitters (e.g., substance P). A deficiency of serotonin and increased activity of substance P could account, in part, for abnormally low pain thresholds in patients with fibromyalgia (16). As a consequence, there is a relationship between low serotonin level and high substance P level in central nervous system in fibromyalgia patients.

Two central nervous system structures are important in fibromyalgia, thalamus and the caudate nucleus (16). The thalamus is known to play an important role in the perception and integration of pain signals, as well as in the generation of signals that regulate the HPA axis (17). The caudate nucleus may be involved in signaling the occurrence of noxious event (18). In a recent SPECT study, Mountz et al (19) shown that patients with fibromyalgia, relative to controls, were characterized by significantly lower rCBF to the left and right hemithalami and the left and right heads of the caudate nucleus. These findings and observations of low pain threshold levels among the patients suggest that abnormal pain perception in fibromyalgia is associated with inhibited functional activity in these structures, especially the thalamus.

SLEEP DISTURBANCES AND POLYSOMNOGRAPHIC FINDINGS IN PATIENTS WITH FIBROMYALGIA

Sleep disturbances are one of key symptoms of fibromyalgia. Patients with fibromyalgia usually report poor sleep quality. They have also an abnormal EEG pattern during sleep. It is very important to evaluate sleep patterns in fibromyalgia patients for treatment of the symptoms.

Sleep Disturbances in Patients with Fibromyalgia

Regardless of the intensity of their pain, most of patients with fibromyalgia suffer from sleep disturbances. They often have unrefreshing sleep, sleep onset, and maintenance insomnia. Sleep studies have suggested that 70% to 80% of fibromyalgia patients complain nonrestorative sleep (20). Poor sleep quality or sleep deprivation may also affect pain and tenderness in patients. In a recent study (21), in patients with fibromyalgia, we administered the Pittsburgh Sleep Quality Index (22) and found that fibromyalgia patients had poor sleep quality.

Recently, May et al (23) reported frequent occurrence of sleep apnea in men with fibromyalgia and suggested that fibromyalgia should be regarded as a marker for sleep apnea. Indeed, both syndromes may be manifested as the same clinical symptoms. Restless sleep, daytime somnolence, morning fatigue, and headache may occur in the patients. Patients with fibromyalgia should be differentiated from sleep apnea patients, particularly in men. However, Alvarez-Lario et al (24) found that only 1 of 30 study patients with sleep apnea met criteria for the diagnosis of fibromyalgia. They concluded that there is no association between sleep apnea and fibromyalgia.

Polysomnographic Findings in Fibromyalgia

In polysomnographic studies, the most common finding is the intrusion of alpha rhythm into NREM sleep (alpha-delta sleep). Patients with fibromyalgia often also exhibit prolonged sleep onset latencies, an increased number of arousals, and increases in stage 1 sleep. Slow wave sleep may be reduced. They may also have altered sleep spindle characteristics.

Alpha-delta pattern

Alpha-delta sleep was first described in 1973 as an unexpected finding during studies of sleep

in patients with various psychiatric disorders. The EEG pattern contained the expected delta waves (amplitude greater than 75 microvolts, frequency 0.5 to 2.0 cycles per second), intruded upon by prominent alpha activity (frequency 7 to 10 cycles per second). In normal individuals, alpha activity is characteristic of drowsy wakefulness, and delta activity indicates restorative NREM sleep.

Twenty-five years ago, Moldofsky et al (25) published a sentinel study describing a slow wave sleep disturbance known as the alpha-delta sleep anomaly in 7 of 10 patients with fibromyalgia. By subjecting 6 healthy volunteers to selective stage 4 sleep interruption, Moldofsky and Scarisbrick attempted to mimic the alpha-delta anomaly, which resulted in the development of fibromyalgia-like symptoms and decreased pain thresholds measured by dolorimetry in all 6 subjects (26). These observations framed the basis for the hypothesis that disrupted slow wave sleep, namely stage 4 disruption, and the presence of alpha activity in slow wave sleep was part of the pathophysiology of fibromyalgia. In a recent study (27), Roizenblatt et al examined the different alpha rhythms during sleep and observed a tendency to superficial sleep among subjects and three different patterns of alpha activity in fibromyalgia: phasic alpha sleep pattern (episodic, occurring simultaneously to delta activity), in 50% of subjects; tonic alpha rhythm (continuous along non-REM sleep, independently of delta activity), in 20% of subjects; and low alpha activity in the remaining.

1) *Determination of observer-rated alpha*

The alpha activity noted during sleep is superimposed on background EEG. In the Toronto clinic, it is described the assessment of such alpha activity as follows (criteria of Moldofsky, personal communication); the following excerpts are taken from the document.

". . . EEG is recorded from C3-A2, C4-A1, Oz-A1 (or A2). Sensitivity is 50 mV and the paper speed is 15 mm/sec. All EEG channels are used to stage the record: alpha activity is assessed from the channel with most alphas. The records are scored in 40 sec epoch using standard criteria."

". . . Alpha activity is defined as frequencies in the range of 7-12 Hz with a minimum peak to peak amplitude of 5 mV. It is rated on a five point scale based on the amount of alpha present: (1) 0-20%; (2) 21-40%; (3) 41-60%; (4) 61-80%; (5) 81-100%. Scorers are instructed not to score alpha activity: (1) when the subject is awake, in stage 1 or in REM; (2) following a movement arousal; and (3) in the presence of artifact. A movement arousal is defined as any epoch containing 5 sec or more of movement arousal artifact. Other artifacts include those produced by sweating, elevated EMG and heart rate."

". . . The records may be assessed in the following ways: (a) while the record is being scored, an assessment of alpha activity during the preceding stage is made at each stage change; (b) after the record is scored a single global rating of alpha is made."

An alpha rating of 1 or 2 is considered clinically insignificant, a rating of 3 is considered moderate and a rating of 4 or 5 is considered severe (28).

Alpha activity recorded during NREM sleep should be differentiated from wakefulness. Generally, alpha activity recorded during NREM sleep is 1 to 2 Hz slower than that of alpha activity recorded during quiet wakefulness. This slower frequency alpha activity is visualized best when recorded from electrodes placed over frontal brain regions. The standard central placement for EEG leads in sleep studies does not permit differentiation of frontal or slower frequency alpha activity from that of occipital or typical waking alpha (29).

2)Is alpha EEG sleep sensitive for the diagnosis of fibromyalgia?

Since the first description by Hauri and Hawkins in 1973 (30), the clinical significance of alpha-delta sleep anomaly is not understood (31). In fibromyalgia, 60-80% of NREM sleep is occupied by this alpha rhythm whereas 25% of NREM sleep is resided in normal subjects or chronic insomniacs (32). However, as many as 60% of patients meeting current criteria for fibromyalgia do not demonstrate alpha-delta sleep (33). Moreover, it was shown poor or no correlation between alpha-delta anomaly and fibromyalgia in several studies (34-40).

3)Is alpha EEG sleep specific for the diagnosis of fibromyalgia?

Alpha intrusion is not peculiar to fibromyalgia and has been reported in the sleep of healthy subjects with no specific sleep complaint (41). Horne and Shackell (35) found no significant difference between the alpha activity of normal control subjects and patients with fibromyalgia. Moreover, it may be suggested that the alpha ratings of normal subjects are greater than those of patients with fibromyalgia (28). The alpha-delta anomaly has been identified in healthy asymptomatic subjects and in a number of other disease states including sleep apnea, nocturnal myoclonus, bruxism, rheumatoid arthritis, osteoarthritis, depression, narcolepsy, and chronic fatigue syndrome (40). Thus, it does appear that alpha-delta sleep is not specific or pathognomonic for the diagnosis of fibromyalgia and may represent an epiphenomenon of an as yet undefined central nervous system disturbance.

Sleep spindle activity in fibromyalgia

Sleep spindles are associated with hyperpolarization of thalamocortical neurons, and are considered critical to maintaining NREM sleep (42). In a recent study, Landis et al

(43) examined sleep spindle characteristics and spindle frequency activity in women with and without fibromyalgia. They found that women with fibromyalgia had fewer spindles of slightly longer duration than control women. They concluded that thalamocortical mechanisms of spindle generation might be impaired in patients with fibromyalgia. These results confirmed Mountz et al's finding of low rCBF in the thalamus and cortex (19) that means an impairment in these structures in fibromyalgia.

THE RELATIONSHIP BETWEEN SLEEP DISTURBANCES AND PAIN IN FIBROMYALGIA

There is a strong relationship between sleep and pain perception in fibromyalgia. In a recent study (44), we examined the association between the sleep quality by assessed using PSQI and pain threshold in fibromyalgia. We found that pain threshold was negatively correlated with the score for subjective sleep quality, habitual sleep efficiency, sleep disturbance, and the PSQI global score. We concluded that increased pain sensitivity is associated with greater sleep disturbance.

Disturbances of slow wave sleep have been associated with a variety of somatic symptoms (45). This association was demonstrated experimentally in both healthy subjects and fibromyalgia patients. The study by Moldofsky et al (25) was the first to explore the association of fibromyalgia-like symptoms and the alpha-delta sleep anomaly. Moldofsky hypothesized that perturbations of NREM delta wave sleep, but no REM sleep, cause lowered pain thresholds and fibromyalgia-like symptoms. Recently, Older et al (40) attempted to replicate the study of Moldofsky et al but did not find significant overnight reductions in pain thresholds. However, all subjects had lower tender point scores in the morning than the prior evening. Lentz et al (29) studied to determine whether deprivation of slow wave sleep would evoke musculoskeletal pain,

fatigue, and an alpha EEG sleep pattern in middle aged women. They found that disrupting slow wave sleep, without reducing total sleep or sleep efficiency, for several consecutive nights was associated with decreased pain thresholds. In a recent study (27), post-sleep increase in tender point's count occurred in 62.5% of fibromyalgia patients and 13.9% of the healthy controls. The phasic, or alpha-delta sleep was associated with worsening of the pain condition after awakening.

Neurobiologic basis of the relationship between pain threshold and sleep in fibromyalgia

The key neurotransmitter is serotonin in underlying basis of the association between pain threshold and sleep in fibromyalgia. Twenty-five years ago, Moldofsky (25) suggested that serotonin deficiency might be an underlying metabolic defect in this disorder. Alterations in substances such as serotonin, endorphins, or substance P may integrate the changes in sleep physiology with symptoms of fibromyalgia (44). Serotonin is recognized as a chemical mediator of deep sleep and pain perception (6); thus, serotonin deficiency and high substance P level in the central nervous system may contribute to sleep disturbance in patients with fibromyalgia. Moreover, both low serotonin and high substance P levels are also associated with pain perception in the patients. High levels of serotonin and its metabolites were found in the hippocampus area in the brain during stage IV sleep in a study (46), suggesting increased synthesis in mammals in the central nervous system during deep sleep. Moldofsky, in his seminal studies of fibromyalgia (26), found a correlation between the nonrestorative sleep reported by most fibromyalgia patients and a characteristic alpha-delta intrusion into stages III and IV sleep. It is also thought that restorative processes occur during slow wave sleep (47) and serotonin deficiency may play an important role in

dysfunction of reparative and restorative processes in the central nervous system in fibromyalgia.

In Yunus's model (15), initial development of fibromyalgia may result from genetic predisposition in combination with one or more precipitating events such as physical trauma, infectious illness, or stressful negative life events. Some events such as infectious illness and muscle injury-related nociception are known to influence neuroendocrine function or to produce increases in substance P and decrease in serotonin levels. Nociception may also negatively affect NREM delta sleep or HPA axis (16). In fibromyalgia, an increase in substance P in the central nervous system, peripheral nerves, and muscles seems a response to the biochemical disequilibrium. Substance P is generated peripherally in the soma builds up and then moves centrally through the nervous system to produce lowered pain thresholds. Serotonin is believed to influence pain thresholds by interacting with substance P and potentiating the effects of endogenous endorphins (15). Lowered pain thresholds allow more pain to be perceived centrally, causing alpha intrusion into deep sleep and disturbing reparative processes, forming a positive feedback loop of dysfunction characterized by decreased flux through the serotonin pathway.

Insulin-like Growth Factor I, slow wave sleep, and pain in fibromyalgia

Eight years ago, low serum levels of Insulin-like Growth Factor I (IGF-I) was described in patients with fibromyalgia by Bennett et al (6). IGF-I is produced in response to GH, which is secreted during slow wave sleep. IGF-I is a hormone that involved in the repair of muscle microtrauma. Thus, there may be an association between low levels of IGF-I and the symptoms of fibromyalgia, particularly pain. Indeed, IGF-I mediates the growth promoting and tissue maintenance functions of GH. It is produced primarily in response to GH secretion. GH is

largely released during slow wave sleep within the first few hours after sleep onset. Thus, the interruption of slow wave sleep inhibits GH secretion, results in decreased production IGF-I. Low levels of IGF-I may result in incomplete repair of muscle microtrauma, leading to the myalgias in fibromyalgia (6). However, in a recent experimental study, Older et al (40) examined the potential correlation between delta wave sleep interruption and serum IGF-I in healthy volunteers. They found that acute delta wave sleep interruption failed to influence serum levels of IGF-I. Thus, it may be suggested that IGF-I in fibromyalgia results from chronic rather than acute delta wave sleep interruption.

Gamma-hydroxybutyrate, the alpha sleep anomaly and pain in fibromyalgia

Gamma-hydroxybutyrate (GHB) is a naturally occurring metabolite of the human nervous system, where it is found in highest concentrations in the hypothalamus and basal ganglia. Although it was shown that GHB promoted both slow wave sleep and REM sleep in healthy persons (48,49), the most consistent effect after administration was an increase in slow wave sleep (50). In addition to increase in slow wave sleep, it was also observed a dose related increase in GH with GHB administration (51). This finding is consistent with GH increase seen association with slow wave sleep. Although it may be expected that GHB levels are lower in fibromyalgia patients than healthy controls, there is no systematic study replicating this hypothesis in the literature. On the other hand, it may be suggested that GHB administration may promote sleep wave sleep and result in an alteration pain thresholds of patients with fibromyalgia. In recent preliminary report, Scharf et al (52) evaluate the effects of using a GHB administered in divided doses at night in 11 patients with fibromyalgia. They found that there was a significant improvement in both fatigue and pain, with an increase in slow wave

sleep and a decrease in the severity of the alpha anomaly. However, limited safety of GHB should not be forgotten.

THERAPEUTIC IMPLICATIONS

Although several well-designed studies of treatment outcomes among patients with fibromyalgia have been published since 1986, there is limited data regarding the effects of treatment interventions on sleep variables in fibromyalgia patients in literature. The research data may be classified into two broad categories: those that evaluate behavioral interventions and those that involve pharmacological treatments. Aerobic exercises, education and physical training, cognitive-behavioral therapy, electromyography biofeedback, and hypnotherapy were found effective in treatment of symptoms such as pain, anxiety, fatigue, and sleep disturbance (for a review see 16). In 1999, Rossy et al (53) evaluated and compared the efficacy of pharmacological and nonpharmacological treatments of fibromyalgia syndrome. When compared, they concluded that nonpharmacological treatment appears to be more efficacious in improving self-report of FMS symptoms than pharmacological treatment alone. They concluded that the optimal intervention for FMS would include nonpharmacological treatments, specifically exercise and cognitive-behavioral therapy, in addition to appropriate medication management as needed for sleep and pain symptoms. A mind-body intervention including patient education, meditation techniques, and movement therapy also appears to be an effective adjunctive therapy for pain, fatigue, and sleeplessness; and improved function, mood state, and general health following an 8-week intervention (54).

Pharmacological studies examining primarily effects of drugs on sleep in fibromyalgia are limited in literature. I will here discuss 5-HTP, antidepressant drugs, 5-HT antagonists, zolpidem, melatonin, and bright light treatment.

5-HTP

5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. In the body, 5-HTP is converted directly to serotonin. Therapeutic use of 5-HTP by passes the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. In a recent double-blind, placebo-controlled study (55), 5-HTP (100 mg three times daily) was given to 50 fibromyalgia patients for 30 days. Sleep patterns together with other symptoms were significantly improved. Two years later, the same group (56) reported on a 90-day open study of 5-HTP, 100 mg three times per day and noted improvement in sleep quality of the patients. Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions except fibromyalgia, including depression, chronic headaches, and insomnia (57).

Antidepressant drugs

Antidepressants, particularly tricyclics, are commonly recommended treatments. In a meta-analysis, Arnold et al (58) reviewed randomized, controlled trials of antidepressants for treatment of fibromyalgia by methodology, results, and potential predictors of response. Twenty-one controlled trials, 16 involving tricyclic agents, were identified; 9 of these 16 studies were suitable for meta-analysis. Measurements of physician and patient overall assessment, pain, stiffness, tenderness, fatigue, and sleep quality were considered. They found that, compared with placebo, tricyclic agents were associated with effect sizes that were substantially larger than zero for all measurements. They suggested that the largest improvement was associated with measures of sleep quality.

Amytriptyline is superior to placebo in improvement in sleep quality. Carrette et al (59) administered 50 mg amytriptyline and found

significantly improvement in sleep qualities of their fibromyalgia patients. More recently, Carette et al (60) evaluated the alpha NREM sleep anomaly as a predictor of response to amitriptyline in patients with fibromyalgia in a 2-month, double-blind, crossover trial of amitriptyline (25 mg/day) versus placebo. They found that 27% of patients had a clinical response to amitriptyline, while none responded to placebo. They also found that treatment with amitriptyline or placebo did not result in any changes in the alpha ratings during NREM sleep. They concluded that alpha NREM sleep anomaly was present in only a small proportion of patients with fibromyalgia and it did not correlate with disease severity nor is it affected by treatment with amitriptyline. In a randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder (61), amitriptyline was found more effective in treatment of pain, sleep quality and quantity, and fatigue on visual analogue scales. The authors indicated that moclobemide may not be helpful in fibromyalgia patients free from clinically meaningful psychiatric problems.

Fluoxetine, a SSRI, was not found superior than placebo in sleep quality of patients with fibromyalgia in a double-blind placebo controlled study (62). However, Goldenberg et al (63) studied the effect of fluoxetine and amitriptyline, alone and in combination, in patients with fibromyalgia and found that both agents were associated with significantly improved sleep disturbances and when combined, the 2 treatments worked better than either medication alone.

Trazodone has 5-HT₂ and α 1-adrenergic antagonism properties and weak serotonin reuptake blocking potency (64). In depressed patients, this drug has been shown to improve sleep continuity and increase slow wave sleep (65). Recently, we (66) compared efficacy of trazodone with placebo in treatment of sleep disturbances in fibromyalgia. We evaluated

sleep quality by the Pittsburgh Sleep Quality Index and found that trazodone was superior to placebo in improvement of sleep quality in patients with fibromyalgia.

5-HT antagonists

The application of 5-HT-receptor-antagonists may be a new strategy for the common treatment of sleep disturbance and the pain syndrome. Serotonergic system has been proved to play a major role in the regulation of both sleep and pain, 5-HT-receptor-antagonists have been used in fibromyalgia patients, at least five years. Hemmeter et al (67) recorded the sleep EEG of 13 patients with a fibromyalgia syndrome in order to objectively characterize their sleep and attempted to beneficially influence the sleep disturbance and the pain syndrome with the 5-HT₂-receptor antagonist ketanserin. They found, in patients with fibromyalgia, disturbance of sleep continuity was associated with the experience of pain intensity. However, in a double-blind manner the effect of the long-acting 5-HT₂-receptor blocker Ritanserin on clinical symptoms in patients with fibromyalgia, there was no difference in pain, fatigue, sleep, morning stiffness, anxiety and tender point counts in the Ritanserin and placebo groups (68). Tropisetron, a 5-HT₃ serotonin antagonist, was investigated in women suffering from primary fibromyalgia (69). A half of patients showed a statistical clinical improvement of pain score, fatigue, sleep disturbances and measurement of the number of tender points.

Zolpidem

Moldofsky et al (70) examined whether zolpidem would improve the disturbed sleep, fatigue, mood and pain symptoms in patients with fibromyalgia in a double blind, placebo controlled, modified crossover study. Compared to the placebo group, they found that patients treated with zolpidem recorded significantly reduced time to fall asleep,

increased sleep time, reduced awakenings, overall improvement in sleep and daytime energy, but a lower rating for evening energy. Zolpidem at the 10-mg dose was rated most acceptable for sleep. As a consequence, they suggested that short-term treatment with zolpidem (5 to 15 mg) did not affect the pain of FM, but is useful for sleep and daytime energy in this patient population.

Melatonin

In a recent study (71), nocturnal urine 6-sulphatoxymelatonin, a melatonin metabolite, levels were found similar in patients with fibromyalgia and control persons. In this study, no association was observed between urine 6-sulphatoxymelatonin levels and disease duration, sleep and mood disorders. Citera et al (72) examined the possible effect of melatonin treatment on disturbed sleep, fatigue and pain symptoms observed in fibromyalgia patients. They were measured urine 6-sulphatoxymelatonin levels in the patients and age- and sex-matched controls. They found that median values for the tender point count and severity of pain at selected points, patient and physician global assessments and VAS for sleep were significantly improved with melatonin treatment. However, their preliminary results should be replicated by double-blind placebo controlled studies.

Bright light treatment

In a recent study Pearl et al (73) investigated the effects of bright light treatment on the symptoms of pain, mood, and sleep in patients with fibromyalgia reporting seasonality of symptoms on the Seasonal Pattern Assessment Questionnaire (SPAQ). They performed a randomized 10 week crossover study compared the effects of 4 weeks of "visible electromagnetic fields" to 4 weeks of "nonvisible EMF" (no light condition) in 14 patients with fibromyalgia having a minimum SPAQ score of 11. They

found no significant differences between the light and no light conditions on pain, mood, or sleep in patients with FM reporting seasonality of symptoms.

CURRENT CONCEPTS AND FUTURE RESEARCH

Immune system, pain, and sleep in fibromyalgia

Neuroimmunoendocrine dysregulation has been considered in the etiology of fibromyalgia. The characteristic symptoms of pain, fatigue and sleep disturbances results from abnormalities in neurochemical and immunological variables in patients with fibromyalgia. Recent studies have indicated a lowered natural killer cell activity as well as abnormalities in lymphocyte populations in fibromyalgic patients (74-76). In a study, significant negative correlations for secondary somatosensory cortex, and insignificant or borderline significant negative correlation for several brain regions, were observed in relation to natural killer cell activity (77). A similar pattern is related to characteristics of the fibromyalgia syndrome and deviations in lymphocyte variables assumed in fibromyalgia (76). Wik et al (78) correlated regional cerebral blood flow measured with [15O] butanol positron emission tomography to immune function in five patients with fibromyalgia. They found that in healthy volunteers, natural killer cell activity correlated negatively with right hemisphere activity in the secondary somatosensory and motor cortices as well as the thalamus. They suggested that immune parameters were related to activity in brain areas involved in pain perception, emotion, and attention.

There is also a growing interest for relationship between sleep and immune system. The migration and distribution of lymphocytes can be influenced by the activity of the central nervous system. Sleep-related changes in cytokines, hormones, and neurotransmitters have the potential to alter

migration patterns of lymphocytes (79). Interleukin (IL)-1 activity and IL-1 beta are elevated in the cerebrospinal fluid of cats during slow-wave sleep (80). IL-1- and IL-2-like activity is found higher during sleep than wakefulness in humans (81). Moldofsky et al (82) and Irwin et al (83) reported a decrease in natural killer activity in response to sleep deprivation. Moreover, Moldofsky et al (84) demonstrated elevated levels of IL-1 activity during slow wave sleep; although this was not replicated by two recent studies (85,86). A disruption in slow wave sleep may result in changes in immune system in fibromyalgia patients. Thus, the relationship between immune system and sleep disturbance may explain etiopathogenesis of fibromyalgia.

Dickstein et al (79) found a decrease in lymph flow during sleep in sheep and suggested that this decrease could be explained by decrease in autonomic nervous activity. They concluded that their observations would be consistent with reduced sympathetic activity during slow wave sleep. Indeed, pathways through which the immune system can affect cerebral activity have recently been described. Cytokines released by immune cells activate vagal afferents, which probably results in cytokine synthesis in the brain (87). On the other hand, immune parameters may be related to the emotional pain component of fibromyalgia. Studies are needed to investigate immune system, pain and sleep in patients with fibromyalgia.

Effects of antidepressant drugs on sleep in fibromyalgia

There is no sufficient data on the effects of antidepressant drugs on sleep-wake cycle in patients with fibromyalgia. Although tricyclic antidepressants have been commonly prescribed in fibromyalgia patients, the effects of novel antidepressants such as SSRIs, mirtazapine, venlafaxine, and venlafaxine on sleep architecture in fibromyalgia patients were not studied systematically. These drugs have

significant effects on slow wave sleep. Citalopram, a novel SSRIs, significantly decreased the EEG power of the NREM mainly in the 8 to 9Hz ranges (lower alpha-waves) without changing the power of the delta frequency range (88). Mirtazapine, known as a noradrenergic and specific serotonergic antidepressant (NaSSA), has presynaptic α -2 autoreceptors and α -2 heteroreceptors antagonist properties. It causes an increased release of both norepinephrine and serotonin, and enhances noradrenergic and serotonergic neurotransmission. Mirtazapine also potently blocks 5-HT₂ and 5-HT₃ receptors. It is thought that mirtazapine's ability to increase deep sleep is also related to its 5-HT₂ receptor antagonism (89). Previously, it was shown that 5-HT-receptor-antagonists were effective in improvement sleep disturbances in fibromyalgia (67,69). Serotonin, and in particular the 5-HT_{2c} receptor, plays a critical role in the regulation of slow wave sleep (90). It can be suggested that the ability of antidepressant drugs to enhance slow wave sleep reflects their 5-HT_{2c} antagonist properties. The fact that 5-HT₂ receptors are upregulated in major depression could explain why some antidepressants such as amitriptyline and mianserin elicit slow wave sleep enhancement in healthy controls but not in patients with major depression (91). It may be suggested that fibromyalgia is a form of major affective disorder or that depression may predispose some individuals to develop fibromyalgia (16). The patients with fibromyalgia also were characterized by high familial prevalence of major depression. On the other hand, fibromyalgia is an affective spectrum disorder and shares a common pathophysiology (92). Thus, it is very important to examine effects of antidepressant drugs on sleep architecture of fibromyalgia patients. Treatment studies with serotonergic antidepressants may also clarify the underlying mechanism of the association among pain perception, sleep-wake disturbances and neurotransmitters in fibromyalgia.

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