Current treatments to counter sleep dysfunction as a pathogenic stimulus of fibromyalgia

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Keywords
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- Non-refreshed sleep is a common symptom in fibromyalgia.
- Polysomnography showed reduced slow-wave sleep and alpha waves during non-rapid eye movement sleep in patients with fibromyalgia.
- Epidemiological studies suggested poor quality sleep in normal population is a risk factor for the development of chronic widespread pain.
- In healthy individuals, disrupting sleep impaired pain processing with reduction in descending pain modulation and led to fibromyalgia-like symptoms.
- Improving sleep quality is associated with reduction in pain.
- Among currently available pharmacological treatments, evidence suggested amitriptyline and pregabalin improve sleep in fibromyalgia

Fibromyalgia is characterized by chronic widespread pain, fatigue and nonrestorative sleep. Polysomnography showed reduced short-wave sleep and abnormal alpha rhythms during Non-rapid eye movement sleep in patients with fibromyalgia. However, sleep dysfunction might be pathogenic in fibromyalgia since myalgia and fatigue could be induced in healthy individuals by disrupting sleep. Poor sleep quality was a major risk factor for the subsequent development of chronic widespread pain in healthy pain-free individuals. Sleep disruption leads to impairment of the descending pain inhibition pathways. Aside from good sleep, hygiene, exercise can promote sleep. Among currently available pharmacological treatments, evidence suggests amitriptyline and pregabalin can improve sleep in fibromyalgia

Background
Fibromyalgia is a common cause of chronic musculoskeletal pain [1]. The condition is not new but the diagnosis has been made more frequent since the publication of the American College of Rheumatology (ACR) criteria in 1990 [2]. The 1990 ACR 'classification' criteria for fibromyalgia required the presence of bilateral pain above and below the waist for at least 3 months as well as the presence of at least 11 out of 18 tender points. Although the main objective of the ACR 1990 criteria was to facilitate research by defining a homogenous patient population, they have been used routinely in clinical practice. Based on the ACR 1990 classification criteria, the prevalence of fibromyalgia in the general population ranges from 0.5 to 4%. Initially, the diagnosis of fibromyalgia had been controversial, however, the publication of several national guidelines by the American Pain Society [3], European League Against Rheumatism [4], German Pain Society [5] and Canadian Pain Society/Canadian Rheumatology Association [6] have established the clinical standards for diagnosis and management

Tender points & tenderness in fibromyalgia
The inclusion of tender point count as a criterion for ACR 1990 classification criteria led to its Although widely used, some studies have questioned their diagnostic validity. One of the key criticism is that fibromyalgia is a polysymptomatic condition. Aside from pain, other symptoms including fatigue, nonrestorative sleep and cognitive impairment are common. Fatigue and nonrestorative sleep affects over 70% of patients with fibromyalgia who often complain of waking in the morning not 'refreshed' and feeling tired. Indeed, they may sleep through the night but still feel fatigue in the morning [7]. Daytime somnolence is common. In 2011, preliminary diagnostic criteria for fibromyalgia was published [8,9] which removed the requirement for the presence of tender points. Instead, patient must meet criteria for a sufficiently high symptom severity scale (SSS) score. SSS score is composed of fatigue, non-refreshed upon waking and cognitive symptoms plus the extent of somatic symptoms. The 2011 preliminary criteria recognized the importance of these symptoms in the manifestations of fibromyalgia. Non-refreshed upon waking is a key feature of poor sleep quality.

Current treatment of fibromyalgia

Treatment for fibromyalgia is a major unmet medical need. Current treatments alleviate symptoms but do not lead to remission. In most patients, a multidisciplinary approach, combining nonpharmacological and pharmacological treatments, is needed [10]. Medications recommended for the treatment of fibromyalgia include simple analgesia, tramadol and tricyclic antidepressants [11] such as amitriptyline as well as three medications that have been approved by the US FDA for the treatment of fibromyalgia in North America: pregabalin and two serotoninnorepinephrine reuptake inhibitors (SNRIs: milnacipran and duloxetine [12]. Gabapentin, a structural analog of pregabalin, is approved for the treatment of neuropathic pain and also commonly used in treatment of fibromyalgia.

Abnormal pain processing in the pathophysiology in fibromyalgia

Although there have been controversies about the diagnostic utility of tender point count in fibromyalgia, increased 'tenderness' is a consistent observation. Patients experience pain to light pressure/touch, which is indicative of allodynia, a feature of abnormal pain processing [13]. In fibromyalgia abnormal pain processing attributed to central sensitization has been demonstrated by many studies [14–19]. Neuroimaging using functional MRI (fMRI), in patients with fibromyalgia and healthy individuals, found similar neuronal activation corresponding to patient reported pain severity. However, in patients with fibromyalgia, lower pressure was needed to elicit the same neural activity [20]. Abnormalities in both the ascending and descending pain pathways have been implicated in the pathogenesis of central sensitization in fibromyalgia. Elevated levels of glutamate, substance P and NGF were found in cerebral spinal fluid [21–24] and decreased cortical gray matter density had been detected in higher brain regions [25–32]. These studies suggested abnormalities in the ascending pain pathway. Other studies have found abnormalities implicating the descending inhibitory pathways with reduced levels of serotonin and norepinephrine in the cerebral spinal fluid [33], which probably accounts for the efficacy of antidepressants, especially SNRIs. Reduced activity in the rostral anterior cingulate cortex, a region of the brain associated with the descending pain inhibitory pathways has been demonstrated by fMRI scan in patients with fibromyalgia compared with healthy controls [34]. Positron emission tomography also found reduced μ-opioid receptor binding potential in the rostral anterior cingulate cortex [35], provided objective evidence that pain processing is impaired in fibromyalgia given the vital role of endogenous opioids pathway in pain modulation. In addition, in fibromyalgia, abnormalities in the inhibitory conditioned pain modulation (ICPM) pathways have also been shown [36–39]. Since pain facilitation from the ascending pathways are strongly linked to the descending pain inhibitory pathways, their relative contribution in the pathophysiology of fibromyalgia remains unclear

The role of sleep in pathogenesis of fibromyalgia

Disturbed sleep is common in patients with fibromyalgia [40]. Wakening feeling nonrefreshed is included in the SSS score of the 2011 preliminary fibromyalgia diagnostic criteria. Patients and physicians have presumed disturbed sleep is a consequence of pain until Moldofsky *et al.* found that in healthy individuals disrupting sleep by auditory stimuli during short-wave sleep (SWS) induced myalgia, fatigue and reduced pressure pain threshold [41]. Subsequently, many studies have implicated sleep in the pathogenesis of fibromyalgia. First, poor sleep quality is associated with worsening of pain and fatigue in fibromyalgia [42]. Second, sleep disturbance aggravates the effect of pain on fatigue and mood. Path analysis found that a night of poor sleep led to worsen pain and mood with reduced physical functioning [43]. Third, poor sleep quality predicts development of fibromyalgia in healthy individuals. In a study of 12,350 painfree women from Norway, 327 developed fibromyalgia. Poor sleep quality was associated with increased risk of developing fibromyalgia in a dose-dependent manner [44]. A recent UK study in 4326 healthy subjects also found nonrestorative sleep was strongest predictor of subsequent development of widespread pain after adjusting for psychosocial factors [45].

Sleep dysfunction in fibromyalgia

Sleep is divided into two main stages: rapid and nonrapid eye movements. Nonrapid eye movement is further categorized into light, intermediate and SWS. The latter is essential to feeling refeshed upon awakening. Polysomnography studies in fibromyalgia found that SWS was reduced and interrupted [46,47]. In healthy individuals, the duration of SWS is directly dependent on the period of prior wakefulness. Prolonged arousal will extend duration of SWS. In patients with fibromyalgia, prominent alpha waves have been found during nonrapid eye movement, especially SWS. Since alpha waves are associated with wakefulness, they have been hypothesized to represent an arousal or awakening state in fibromyalgia [48].

Disturbed sleep impairs pain processing

The potential role of sleep disturbance in the pathogenesis of fibromyalgia has been strengthened by recent studies showing that disruption of sleep could impair pain processing. In healthy individuals, disrupting sleep reduce activity in descending inhibitory pain pathways [49–52]. Restoration of sleep improves pain with increase in pressure pain threshold to normality. Chronic pain is more common in patients with primary sleep disorders such as narcolepsy and cataplexy than the normal population [53]. In these patients, sleep and depression were major determinants on severity of pain.

Effect of current treatment for fibromyalgia on sleep
A recent systematic review and meta-analysis examined the effect of current nonpharmacological and pharmacological treatment on different core symptoms of fibromyalgia [54]. Studies on nonpharmacological treatments often combined several treatments. There is low-quality evidence to suggest exercise, cognitive–behavioral therapy and balneotherapy might improve sleep. For pharmacological interventions, low-dose amitriptyline had a moderate effect on improving pain, sleep and fatigue but no effect on mood. The effect of other anti-depressants, which include SNRI (milnacipran, duloxetine) and selective serotonin reuptake inhibitors (SSRIs; citalopram and fluoxetine) were small with effect sizes of less than 0.3. For SNRI, improvement in sleep was not statistically significant. Pregabalin had a small effect on pain (effect size: 0.31) but moderate effect on sleep (effect size: 0.57). However, caution is needed to interpret these data since the patient populations enrolled in these trials were different. Many patients recruited to trials of SNRI, SSRI and pregabalin had previously failed amitriptyline so direct comparison between SNRI, SSRI and pregabalin versus
amitriptyline should be avoided.

Effect of SNRI on sleep
A secondary analysis of duloxetine on fatigue and sleep in patients with fibromyalgia found that duloxetine versus placebo statistically significantly reduced fatigue, pain, anxiety, depressed mood and stiffness. Improvement in the rating of 'being bothered by sleep difficulties' was significant only at week 4 and 8 [55]. A study on milnacipran using polysomnography found that milnacipran did not improve 'wake after sleep onset' or 'number of awakenings after sleep onset' but reduced sleep efficiency [56]. Together these data suggested that SNRI improved sleep by reducing pain rather than having a direct effect on sleep.

Effect of pregabalin on sleep
Pregabalin was developed initially as an anticonvulsant and subsequently approved for the treatment of anxiety, neuropathic pain and fibromyalgia. A pool analysis of Phase II and III randomized control trials of pregabalin in fibromyalgia found that pregabalin reduced pain and improved sleep quality [57]. A subsequent randomized placebo-controlled trial of pregabalin in 197 patients with fibromyalgia with comorbid depressant and taking concurrent anti-depressants (SNRI or SSRI) [58] also found that pregabalin reduced pain, anxiety and depression as well as improved sleep quality when compared with placebo-treated patients. However, these results were based on patient's report of sleep quality. In a recent randomized, placebocontrolled, crossover trial, 119 patients with fibromyalgia with disturbed sleep defined as wake after sleep onset ≥45 min and total sleep time of 3–6.5 h received either 150–450 mg/day of pregabalin or placebo [59]. Polysomnography was performed for two consecutive nights at screening and post-treatment. Pregabalin decreased number of wake/sleep bouts (-3.61 min; $p = 0.0039$) and increased sleep bout duration (+3.67, min; $p < 0.0001$). Slow-wave sleep correlated positively with sleep bout duration and negatively with wake/sleep bout number. The result of this study suggested pregabalin improved sleep quality with an increase in 'deep sleep'. The results from these studies were supported by a systematic review and indirect comparison of pharmacological treatments for fibromyalgia, which found pregabalin, milnacipran and duloxetine reduced pain and improved physical function [60]. However, pregabalin produced statistically significantly greater improvements in sleep compared with milnacipran. Dosing of pregabalin and SNRI was based on pharmacokinetics and adopted from their use in other indications such as anxiety and depression. For improving sleep, it may be more effective if they are taken as a single dose in the evening. This should be examined in future clinical trial.

Trials of sleep modifiers in fibromyalgia
Good sleep hygiene practices should be recommended to patients with fibromyalgia with nonrestorative sleep. These include avoiding stimulants (such as caffeine), large meals and alcohol too close to bedtime. Although alcohol can speed the onset of sleep, it disrupts sleep in the second half of the night. Exercise can promote sleep. As yet, no current recommended medication for the treatment of fibromyalgia is known to reverse all polysomnographic abnormalities associated with fibromyalgia [61].

Benzodiazepines
Benzodiazepines such as zolpidem and zopiclone are commonly prescribed medications for insomnia. However, they have no or limited effect on sleep architecture and do not affect SWS [62,63]. Indeed, most patients with fibromyalgia do not complain of insomnia, but disturbed sleep such as frequent awakening at night [1]. Randomized control trials of zolpidem and zopiclone found limited efficacy in fibromyalgia [64,65]. Polysomnography study of ziploclone confirmed it has no effect on sleep architecture.

Sodium oxybate
Sodium oxybate is a sleep modifier licensed for the treatment of excessive daytime sleepiness associated with narcolepsy. It is metabolized to gamma-hydroxybutyrate, and acts as an agonist of the gamma-

aminohydroxybutyrate and gamma-hydroxybutyrate receptors. It improves sleep architecture [66] but has no known effect on pain. Hitherto, it is the only treatment, which has been trialed in fibromyalgia that targets specifically sleep dysfunction. Several randomized placebo-controlled trials of sodium oxybate have been conducted in fibromyalgia [67–70]. Sodium oxybate reduced sleep disturbance and fatigue with a medium effect size. It also reduced pain with effect size at least comparable to current recommended treatment such as tricyclic antidepressant. A path analysis confirmed that sodium oxybate had no direct effect on pain. Reduction in pain was almost entirely mediated by improvements in sleep [71]. However, the prescription of sodium oxybate is highly controlled and regulated. It is fast-acting and induces deep sleep. Fallen in the wrong hands, it has been used as a date rape drug. Hence, it is not recommended for the treatment of fibromyalgia. However, these studies are mechanistically important. If sleep dysfunction is secondary to pain, then sodium oxybate should improve sleep but not pain. The therapeutic effect of sodium oxybate on pain suggests sleep dysfunction has an important role in abnormal pain processing in fibromyalgia.

Melatonin

Melatonin is a hormone released from the pineal gland during darkness. It regulates sleep–wake cycle. Melatonin is available as an over-the-counter medicine in North America which has been used commonly for reducing jet lag and shift workers to adapt to sleeping during the day. In many countries, melatonin is a prescription-only medicine used for treating insomnia or sleep dysfunction associated with a variety of disorders. A systematic review and meta-analysis of melatonin in 1683 patients with primary sleep disorders from 19 studies found that melatonin demonstrated significant efficacy in reducing sleep latency and increasing total sleep time [72]. Overall sleep quality was significantly improved in subjects taking melatonin compared with placebo although the absolute benefit was smaller than other pharmacological treatments for insomnia. However, the correct dosage of melatonin needed to treat sleep dysfunction is unclear [73]. Some research suggested that lower doses (0.3–1.0 mg) may be more efficacious than the commercially available doses which are three- to ten-times normal level in the body. Furthermore, higher doses of melatonin may have side effects, which include headache, short-term feelings of depression, daytime sleepiness, dizziness, vivid dreams and nightmares. Shorter term used of melatonin is safe but side effect after regular long-term usage is not known.

In a control trial of melatonin in 63 patients with fibromyalgia, patients were randomized to receive 25 mg amitriptyline, 10 mg melatonin or a combination of both for 6 weeks [74]. Melatonin alone or in combination with amitriptyline reduced significantly pain and increased the inhibitory pain-modulating system as assessed by conditional pain modulation by hot heat task and pressure pain threshold. Combining melatonin with amitriptyline led to greater improvement in physical functioning. Sleep quality as assessed by the Pittsburg Sleep Questionnaire showed similar improvement with melatonin alone, amitriptyline alone or a combination of both.

A number of melatonin receptor agonists, ramelteon and tasimelteon have been developed and approved for the treatment of sleep disorders. Their therapeutic potential in fibromyalgia should be explored in randomized placebo-controlled trial.

Cyclobenzapine

Cyclobenzapine was found to be effective in reducing pain and improving sleep in a 12-week double-blind randomized control trials in patients with fibrositis [75]. Three double-blind, randomized placebo-controlled trials reported that cyclobenzaprine was more effective than placebo in alleviating symptoms of fibromyalgia and improving sleep [76–78]. A meta-analysis of fivestudies suggested that cyclobenzaprine had moderate beneficial effect on individual symptoms, particularly sleep [79]. A recent small double- blind, placebo-controlled, dose-escalating study evaluated the short-term effects of very low-dose cyclobenzaprine in patients with fibromyalgia after 8 weeks on sleep using polysomnography [80]. Compared with placebo-treated patients, cyclobenzaprine improved pain, fatigue, tenderness and depression. Polysomnography showed that cyclobenzaprine increased number of nights of restorative sleep. Large Phase III trial of cyclobenazpine will be needed to establish its therapeutic role in fibromyalgia.

Nabilone

Several cannabinoids have been developed for the treatment of chronic pain. Nabilone is a synthetic cannabinoid, which has been studied in fibromyalgia. A double-blind randomized crossover trial compared the short-term effect of nabilone on sleep with low-dose amitriptyline in 31 patients with fibromyalgia and chronic insomnia for 2 weeks [81].

Nabilone was superior to amitriptyline as assessed by Insomnia Severity Index and restfulness but not on wakefulness. However, no effects on pain, mood or quality of life were observed in this short study.

Conclusion

Fibromyalgia is a common cause of chronic widespread pain in which nonrefreshed sleep is a common symptom. Polysomnography found reduced slow-wave sleep and intrusion of alpha waves suggestive of a lack of 'deep sleep'. Although severe pain may lead to sleep dysfunction, both epidemiological and experimental studies have suggested sleep dysfunction may lead to the development of fibromyalgia. In healthy individuals, sleep disruption impairs pain processing with reduction in descending pain modulation. among currently available pharmacological treatments, there is evidence to suggest amitriptyline and pregabalin can improve sleep quality. Trials of sodium oxybate showed that improving sleep could reduce pain and fatigue and therefore key symptom domains in fibromyalgia. This is an important therapeutic strategy for developing new treatments for fibromyalgia. However, new treatment must improve sleep architecture. Polysomnographic evidence demonstrating effect of treatment on sleep architecture is important during clinical development of new treatments. Currently, there are few medications that can improve sleep architecture. Melantonin receptor agonists and cyclobenzaprine showed promise in preliminary studies but more detailed studies will be needed to establish their effect of sleep and pain in fibromyalgia.

Future perspective

Traditionally, sleep disturbance is considered to be a consequence of pain. In fibromyalgia, there is sufficient evidence to suggest improving sleep quality may be an effective treatment strategy. While treatments such as benzodiazepines are available for insomnia, they do not improve or prolong SWS. Trials of cyclobenzaprine will inform further improving sleep quality is effective treatment strategy in fibromyalgia. If successful, it may drive further pharmaceutical development.

Financial & competing interests disclosure

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