Review

Transdiagnostic factors across fibromyalgia and mental disorders: sleep disturbances may play a key role. A clinical review

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ABSTRACT

Sleep disturbances, affective disorders, pain and fatigue are often present in individuals affected by fibromyalgia (FM). The pathophysiology of FM is not yet well understood and, to date, no treatment has been proven to be fully effective in alleviating all symptoms. Adopting a transdiagnostic perspective could thus be useful for clinicians: treatment would target a transdiagnostic process across a range of disturbances, not just a single disorder. The aim of this review is to revise the available literature about the potential role of sleep disturbances as a transdiagnostic process in FM symptomatology and mood or anxiety disorders comorbidity. We are proposing a model under which sleep disturbances can play a central role. Because conditions of sleep loss are related to the activation of the stress system, including the activation of the inflammation system, we propose this mechanism as a key one: it can be shared by mental, sleep disturbances and pain in FM and it may explain, in part, the high levels of comorbidity between them. In this framework sleep disturbances may play a key role and be the target of therapeutic strategies across FM symptomatology and mental disorders.

Introduction

Fibromyalgia (FM) is a chronic multisymptom complex syndrome characterised by persistent widespread pain of the muscle and connective tissues, and pain in response to touch or pressure (1-3). In addition, fatigue, sleep disruption, difficulty in memory, concentration and psychiatric disturbances are described as cardinal characteristics (1-5). The estimate for lifetime prevalence of FM is approximately 2% in community samples, and the prognosis for symptomatic recovery is generally poor (2, 6, 7). FM has a substantial negative impact on daily life, limiting patients' functioning and negatively affecting emotional well-being (8, 9). As it largely affects a working-age population, and is associated with increased resource use and disability, FM is responsible for substantial social costs (10). Patients report that FM symptoms substantially impact their quality of life by disrupting relationships, causing social isolation, reducing productivity in activities of daily living, and complicating physical activity (11). The syndrome pathology is not well understood, and to date, no treatment has proven to be effective in fully alleviating its symptoms (12-15).

Understanding the mechanisms involved in FM may thus be particularly useful to design effective prevention and treatment strategies, that may also address its comorbid conditions. Sleep problems and disrupted sleep are highly related to FM (5, 11, 16) and directly to both fatigue and pain (5, 11, 16, 17). Insomnia and poor sleep quality have emerged as major determinants of psychic and somatic health, including rheumatologic disorders (18-26) and (18, 27).

Disordered sleep is such a prominent symptom in FM that the American College of Rheumatology included symptoms such as waking unrefreshed, fatigue, tiredness, and insomnia in the 2010 diagnostic criteria for FM (1, 27). The possible role of sleep disruption in FM on pain, inflammation and cytokines has been also hypothesised (18, 28-31). Sleep loss and disturbed sleep have been related to the hyper-activa-

tion of the stress system (26), including the inflammatory system activation (18, 22, 28-31). On these bases a reciprocal relationship between sleep disturbances and pain has been hypothesised, with sleep deprivation modulating pain, and pain disrupting sleep, a vicious cycle of perpetuation and augmentation which can arise through the stress system activation (18, 20, 23).

Sleep disturbances have been also hypothesised to play a major role in the relationship between pain, anxiety, stress related conditions and depression, some of the most frequent psychiatric comorbidities in FM. The impact of chronic pain on emotional variables, in fact, seems to be mediated by subjective sleep quality and low sleep efficiency (33).

FM patients often complain multiple mental problems that are related to a more severe course of FM and directly to pain and fatigue, particularly anxiety, mood, post-traumatic stress and disorders (17, 34-44). Dysfunctional bidirectional pathways between the brain and the immune, endocrine and neurotransmitter systems have been extensively described and implicated in pain and psychiatric disorders (35, 38). Chronic inflammation and the stress system activation may provide an important link between chronic pain and affective disorders, and the possible cellular mechanisms involved in this process (35, 38, 45-47).

The high degree of comorbidity between sleep disturbances and mental disorders in FM may lead to a search for the mechanisms responsible for this comorbidity, referred to as transdiagnostic factors. The transdiagnostic perspective has gained momentum in recent years, and is now a foundational aspect of the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) program (48). RDoC aims to investigate underlying processes across traditional psychiatric disorders. Within the transdiagnostic perspective, a mechanistic transdiagnostic process is causally or bidirectionally related to the psychiatric disorder.

There are a number of advantages for clinicians and researchers in taking a transdiagnostic perspective in FM. Individuals suffering from FM may experience pain, fatigue, mood and sleep disorders; it can thus be challenging for a clinician to decide which disorder to treat first, and the treatment would thus target a transdiagnostic process across a range of disturbances, not just a single disorder.

On these bases, and also because sleep disturbances are frequently associated with anxiety and mood disorders in a very complex relationship (19, 25, 49, 50), insomnia has been proposed as a transdiagnostic process in psychiatric disorders. The aim of this review is to review the available literature on the potential role of sleep disturbances in mood, anxiety disorders and FM symptomatology.

We are proposing a model under which sleep disturbances can play a central role as a transdiagnostic process across mood and anxiety disorders and FM symptomatology, with particular attention to pain and fatigue. As conditions of sleep loss are related to the activation of the stress system, including inflammation, we here propose this mechanism as a key one: it can be shared by mental, sleep disturbances and pain in FM and it may explain, in part, the high levels of co-morbidity between them. In this framework, sleep disturbances may play a key role and be the target for therapeutic strategies across FM symptomatology and mental disorders.

Sleep disturbances and fibromyalgia

Clinical evidences

In a patient Delphi Panel run as part of the Outcome Measures in Rheumatology (OMERACT) project, sleep problems appeared as the fourth most important domain to FM patients with 92% of patients reporting that this domain should be assessed in FM clinical trials (5, 16). In another study, patients with FM reported that disrupted sleep was a common symptom associated with FM (34). In other studies sleep disturbance is described as a part of the FM patient experience (9, 51-53).

Most patients indicated that both fatigue and pain were directly related to the poor quality of their sleep (34). During the 9th annual meeting of OMERACT (5), sleep disturbance was noted as a core set of domains considered essential for assessment in FM clinical trials. The impact FM has on sleep was defined in OMERACT as difficulty falling asleep, staying asleep and unrefreshing sleep (5).

In two comprehensive systematic reviews on the field (54, 55) it emerged that the specific concepts most frequently noted as being a clinical component of FM included: sleep disturbance as increased number of arousals (56), poor sleep quality (57-59), insufficient sleep duration (60), daytime dysfunction (61), awakening unrefreshed (62) and low sleep efficiency (63). Patients with FM were found to be significantly more likely to experience difficulties initiating or maintaining sleep almost 5 times more than controls (64). In particular, difficulty falling asleep, staying asleep and waking up too early in the morning have been identified as the most common sleep-related symptoms among the FM population (64, 65). Sleep-recording abnormalities are characterised by a reduced total sleep time and sleep efficiency, with increased number of awakenings, a reduced amount of slow wave deep sleep and an abnormal alpha wave intrusion in delta deep sleep, termed alpha-delta sleep, suggesting that FM is characterised by an inability to maintain continuous sleep (66-68). Moreover, other microstructural revealed high frequency of arousals and alpha-K complex reported, both indicators of fragmented sleep. A study reported that women with FM have similar nocturnal sleep disturbance as those with rheumatoid arthritis, but FM patients reported greater self-rated daytime sleepiness and fatigue than rheumatoid arthritis patients, which did not correspond to the relatively low level of objectively determined daytime sleepiness of FM patients. These findings suggested the presence of a generalised hyperarousal state in FM, that is a state of cognitive and physiological activation of the hypothalamic and pituitary adrenal axis (HPA) (69).

Poor sleep quality and disturbed sleep have been associated with negative effect on pain, fatigue, mood, disease ac-

tivity, physical functioning and quality of life in FM (5, 9, 11, 16, 17, 39, 59, 68, 70-73).

Psychobiological hypothesis

Poor sleep has a reciprocal relationship with pain (18, 20, 23, 32), as there is evidence to suggest that it is both a consequence (17) and a causal or maintenance mechanism (74, 75) for chronic pain conditions. Sleep duration may also play a relevant role as it has been shown to predict clinical pain in adults with insomnia (76) and sleep disruption has been predictive of next day clinical pain in individuals with a pain condition (74). In addition, poor sleep quality may account for the positive relationship between pain and fatigue in FM, thus playing a mediation role in their relationship in FM (17, 37, 39).

The cognitive activation theory of stress (77) may offer a theoretical framework to understand the possible comorbidity between pain/fatigue and sleep disturbances in FM. The theory proposes that through chronic arousal, stress, and lack of restorative sleep, there are changes in the functioning of the HPA-axis and central nervous system leading to an increased sensitivity to stimulation, particularly pain. Thus, sleep disturbance may be playing an important role in the maintenance of FM chronic pain. In fact, hyperarousal, *i.e.* the hyper activation of the stress system, has been described as a key characteristic of people with disturbed sleep (26).

Additionally, insomnia, poor and disturbed sleep have a very complex relationship with anxiety and depression, resulting in a bidirectional association, mutually favouring each other (24, 49, 50); sleep disturbances have also been related to negative mood in FM (78, 79). Research on the relationship between insomnia and psychiatric disorders demonstrates that insomnia is a mechanistic transdiagnostic process related to the onset and maintenance of major depressive disorder, bipolar disorders and anxiety disorders (80). This kind of relationship may explain the negative effect on mood also in FM. Even in this case, the hyperactivation of the stress system may offer a theoretical framework to understand the possible comorbidity between sleep disturbances and mental disorders, including comorbidities in FM. The cognitive activation theory of stress (77) may also offer a theoretical framework to understand the possible comorbidity between mental disorders and sleep disturbances in FM. Most recent intriguing hypotheses highlight ruminative thoughts to be strongly associated with post-traumatic stress disorder (PTSD) and with some of its core manifestations, such as sleep disruption, suggesting a possible role of subthreshold autism features in these relationships (81-83). Considering the high incidence of multiple traumas in individuals with FM, we may speculate a role for autistic features as a vulnerability factor to post-traumatic stress symptoms, insomnia and pain in these patients.

Mental disorders and fibromyalgia

Clinical evidences

FM patients often complain multiple mental disorders; conversely, increasing evidence suggests mental dysfunctions to belong to the clinical picture of FM. Mental disorders comorbidity includes: major depressive disorder, bipolar disorder, panic disorder and social phobia, reported in rates as high as 62%, 11%, 29% and 19% of FM patients, respectively (34, 36, 42, 84, 85). Interestingly, subthreshold mood and post-traumatic stress symptoms have been described to be prominent in FM (40, 42).

Mental disorders, especially mood disorders, have been associated with negative effect on pain, fatigue, sleep disorders, decrements in physical functioning, and quality of life in FM (17, 34, 35, 37-39, 41-44, 85-89). Moreover, manic spectrum symptoms are correlated to the severity of pain and the health-related quality of life in patients with fibromyalgia (36).

Psychobiological hypothesis

Chronic inflammation and the activation of the stress response system have been shown to provide an important link between chronic pain/fatigue and affective disorders in FM (35, 38, 45-47).

As previously observed, affective disorders have a very complex relationship with sleep disturbances resulting in a bidirectional association mutually favouring each other (24, 49, 50, 90), which may be also present in FM (17, 39). Research on the relationship between insomnia and psychiatric disorders demonstrates that insomnia is a mechanistic transdiagnostic process related to the onset and maintenance of major depressive disorder, bipolar disorders and anxiety disorders (80). The activation of the HPA stress system named hyperarousal has been shown to provide an important link between affective disorders and sleep disturbances. We may hypothesise that this mechanism may play a key role also when sleep disturbances and affective disorders are comorbid conditions in FM.

Conclusion: a hypothesis

Sleep disturbances, affective disorders, pain and fatigue are often present in individuals with FM. The syndrome pathology is not well understood, and to date, no treatment has proven effective in fully alleviating all its symptoms. Adopting a transdiagnostic perspective in FM could be useful for clinicians: treatment would target a transdiagnostic process across a range of disturbances, not just a single disorder. In this framework, sleep disturbances may play a key role. In the present review we have proposed sleep disturbances as a transdiagnostic mechanism across mental disorders and FM symptomatology, in light of they fact that they: 1) are considered a transdiagnostic mechanism in mental disorders; 2) represent a very frequent disorder in FM; 3) mediate the relationship between affective disorders and pain in FM; 4) mediate the

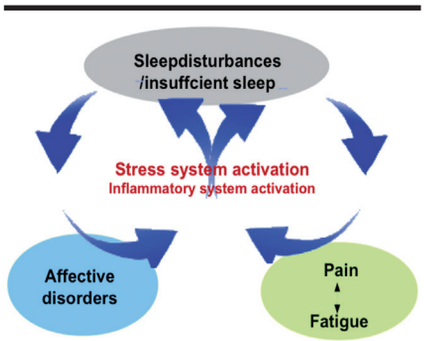

Fig. 1.

relationship between pain and fatigue in FM; and 5) are mutually and bidirectionally linked with FM symptomatology such as pain and fatigue. We may hypothesise that the hyperactivation of the stress system, including the inflammation system, may be the underlying psychobiological mechanism accounting for this type of relationship (Fig 1).

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