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Review

Sleep Dysfunction in Fibromyalgia and Therapeutic Approach Options

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Abstract

Fibromyalgia, characterised by persistent pain, sleep disturbance, fatigue and cognitive dysfunction, is a central sensitivity syndrome that also involves abnormality in peripheral generators and in the hypothalamic pituitary adrenal axis. Heterogeneity of clinical expression of fibromyalgia with a multifactorial aetiology has made the development of effective therapeutic strategies challenging. Non-restorative sleep associated with poor sleep quality is a characteristic of fibromyalgia which is linked to symptom severity. A relationship between sleep disorder and central sensitization could be a possible factor involved in development, exacerbation and/or maintenance of fibromyalgia. Association between disordered sleep and the risk of fibromyalgia suggests that limiting sleep problems would reduce the incidence of the condition. Therapeutic approaches with treatments that consolidate or deepen sleep may be preferential to improve sleep in patients with fibromyalgia. Thus, disordered sleep appears fundamental to the pathophysiology of fibromyalgia and as such the risk of sleep disturbances needs to be proactively assessed and when identified in this patient group be actively managed to improve health outcomes for patients with fibromyalgia.

Keywords
Fibromyalgia; sleep; persistent pain; fatigue; anxiety

1. Introduction

Fibromyalgia is characterised by persistent pain, fatigue, sleep disturbance and cognitive dysfunction (i.e. attentional capacity and memory) with disorder of central pain processing producing heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia) dominating the condition [1, 2]. Co-morbidities of fibromyalgia include psychiatric conditions such as depression and anxiety [1, 2]. Classification of fibromyalgia was originally based on the American College of Rheumatology (ACR) 1990 criteria of widespread pain (for at least 3 months) and pain in 11 of 18 tender point sites [3]. Revision of the criteria in 2010 introduced assessment of the range of symptoms by determination of somatic symptom severity (i.e. sleep disturbance, cognitive dysfunction and fatigue) and widespread pain, avoiding reliance on tender points with further revision in 2016 to limit potential misclassification and introduce a fibromyalgia symptom scale [4, 5]. Worldwide prevalence, based on application of ACR 1990 criteria, of 0.4–8% of the population has been reported, with fibromyalgia being seven times more common in females than males [6].

The pathophysiology of fibromyalgia involves enhanced neuronal excitability, related to central (CS) and peripheral sensitization, presenting amplified responses of the central nervous system (CNS) to peripheral input [2]. Peripheral sensory generators contributing to this heightened activity of the CNS, include nerve pathologies, neuroinflammation, skeletal muscle abnormalities and ischaemia [7, 8]. Systemic stress-related events linked to alterations in the hypothalamic pituitary adrenal axis (HPA), autonomic nervous system and cardiovascular system have also been reported to be underlying or enhancing the symptoms of fibromyalgia [2, 7]. In addition to neuronal sensitization and neuroendocrine dysfunction, oxidative stress, immunological factors and genetics have also been linked with the pathophysiology. The characteristic spectrum of symptoms of fibromyalgia however cannot be accounted for by any of these factors in isolation.

Altered neurotransmitter functioning and neuroplasticity, consistent with an enhanced excitation and reduced inhibition within the CNS leading to augmented sensory processing, has been suggested to contribute to the CS in fibromyalgia [7]. Raised levels of glutamine (2-fold), nerve growth factor (4-fold), brain-derived neurotrophic factor (BDNF, 2 to 4-fold), substance P (2 to 3 fold) and endogenous opioids (3 to 4-fold) are observed in the cerebrospinal fluid (CSF) of people with fibromyalgia compared to healthy subjects [2, 9-11]. In contrast, in people with fibromyalgia lower CSF levels have been reported of the main metabolites of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG), and blood levels of serotonin and L-tryptophan [2, 9].

The combination of pharmacological and non-pharmacological therapeutic approaches is required for the management of fibromyalgia with the approach to drug therapies being empiric with a focus towards individual symptoms, primarily pain [1, 4]. Thus, a primary aim of many of the pharmacological treatments is lowering levels of pronociceptive excitatory neurotransmission and/or increasing antinociceptive inhibitory neurotransmission in the CNS. Current therapeutic

options for fibromyalgia are drugs that raise serotonin and noradrenaline levels in the CNS (e.g. tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors) or target voltage-gated calcium channel $\alpha 2\delta$ subunits (e.g. gabapentin and pregabalin) [1, 4]. The heterogeneity of clinical expression of the spectrum of symptoms of fibromyalgia in combination of a multifactorial aetiology has made the development of effective therapeutic strategies challenging.

The aim of this article is to consider the relationship of fibromyalgia and sleep, with respect to involvement in the pathophysiology or as a treatment approach of the condition. MEDLINE database, Web of Science and Google Scholar were used to identify relevant studies and publications up to August 2019 using the terms 'sleep' and 'fibromyalgia'.

2. Sleep Disturbances in Fibromyalgia

Approximately 90% of patients with fibromyalgia experience sleep disturbance with poor sleep quality strongly associated with symptom severity [12-15]. Complaints concerning sleep include superficial, fragmented and non-restorative sleep, and restless leg syndrome followed by early awakening and morning fatigue [16, 17]. Although sleep quality is poor leading to the enhanced pain and fatigue with patients waking with stiffness and reduced physical functioning, often quantity of sleep of up to 8 hours is experienced [18, 19]. Patients with fibromyalgia report difficulty falling asleep, significantly more night-time awakenings, extended stage 1 sleep, and diminished slow wave sleep during non-rapid eye movement sleep [20-22]. Slow wave sleep is essential to feeling refreshed upon awakening, thus alterations in patients with fibromyalgia will be associated with unrefreshing sleep and arousal or awakening states [23].

Subnormal growth hormone secretion and low levels of somatomedin C have been observed in some patients with fibromyalgia [24, 25]. A loss of growth hormone secretion during slow wave sleep may be linked to abnormalities in dorsal medial nucleus of the thalamus [26]. Abnormal thalamic activity and a lower stimulus threshold for the activation of the pain pathway are manifestations of fibromyalgia at the neural level [27, 28]. Growth hormone and somatomedin C are necessary for the repair of microtrauma; sleep disturbances associated with fibromyalgia may impair the healing of muscle tissue damage which will continue to transmit sensory stimuli to the CNS maintaining the perception of muscle pain. The enhanced pain will contribute to the sleep disturbance which will maintain the inadequate muscle tissue repair.

Heterogeneity has been observed across studies of sleep in fibromyalgia, which may be related to age, body mass index (BMI), tender points, time since diagnosis and assessment methodology [21, 22]. Sleep difficulties in fibromyalgia appear to be greater when reported subjectively, e.g. using Pittsburgh Sleep Quality Index (PSQI), than when assessed objectively, e.g. using polysomnography or actigraphic devices, which may be a consequence of perception and the possibility of catastrophizing being common with this condition [22]. Subjective methods of sleep assessment can include instruments such as the PSQI, the Fibromyalgia Impact Questionnaire and written or electronic sleep diaries which are reliant on self-report and are the involved in the evaluation and treatment of sleep complaints within the clinical setting. Studies have suggested subjective report of sleep quality exhibited a relationship to fibromyalgia symptoms, which was not observed with objective sleep data [29, 30]. Subjective assessment is dependent upon accurate recall and perception of sleep quality rather than evaluation of sleep architecture, which will be influenced by personal and environmental factors (eg fatigue, poor mood) at the time.

Consequently, the level of presentation of fibromyalgia symptoms may lead to greater attribution to sleep disturbance. Thus, therapeutic approaches that target perception (e.g. cognitive-behavioural approach) rather than sleep architecture (e.g. medication) may provide preferable outcomes. Although it would appear preferable to confirm sleep complaints with an objective method, this may not be feasible in a clinical setting. In addition, actigraphic devices, which monitor movement, would record a motionless person as asleep and could misrepresent the bedtime habits of the patient with fibromyalgia.

3. Risk Factors of Fibromyalgia and Sleep Disturbance

Persistent widespread pain being a risk factor of disordered sleep, recorded by polysomnographic, has been reported in studies of patients with fibromyalgia [21, 31]. Patterns of sleep discontinuity and lower sleep efficiency are consistent with the persistent pain being associated with heightened states of arousal during sleep [32]. In addition, disordered sleep and decreased rapid eye movement (REM) sleep is associated with increases in the risk of fibromyalgia symptoms, pain perception and widespread pain [15, 33-37]. More sleep interruption and movement at night with increased sleeping and lower levels of activity during the day have been observed in patients with fibromyalgia when depressed [38]. Depression levels in patients with fibromyalgia have also been suggested to be predictors of subjective sleep quality [21]. In this patient group depression appears to be exacerbated by and contribute to sleep disturbance [39]. The tendency to experience depressive symptoms, as with persistent pain, correlates with hyperarousal indices during sleep leading to sleep complaints [40].

Patients with fibromyalgia have a high prevalence of overweight and obesity which is associated with a higher number of sleep disturbances and painful regions [14, 41, 42]. The prevalence of overweight in patients may contribute to additional sleep disorders such as sleep apnea, inspiratory airflow limitation with arousals and obstructive sleep apnea which can be common in patients with fibromyalgia [43-45]. Alleviation of symptoms has been reported following weight loss in patients with fibromyalgia, whilst reduction of the risk of fibromyalgia is associated with regular physical activity [46-48]. In patients with obstructive sleep apnea treatment with continuous positive airway pressure exhibited beneficial in patients with fibromyalgia [49]. Lifestyle factors have therefore been proposed to influence the association between insomnia symptoms and risk of fibromyalgia [50]. Self-reported physical activity intensity levels have been associated with sleep quality in women with fibromyalgia [51]. Higher physical activity levels and lower sedentary time are associated with reduced symptoms in patients with fibromyalgia [52, 53]. In a cross-sectional study of women with fibromyalgia, more sedentary time was associated with significantly worse subjective sleep quality, sleep duration, sleep disturbance and daytime dysfunction assessed by the PSQI [54]. Better subjective sleep quality, sleep latency, sleep medication and daytime dysfunction were correlated with physical activity, whether light, moderate or moderate-to-vigorous. Thus, women with fibromyalgia who engage more physical activity (recommendations of 150 minutes/week of moderate-to-vigorous physical activity in bouts $\geq$ 10 minutes) and present less sedentary time, pain and anxiety appear to have improved night-time sleep and feel less sleepy during the day. In fibromyalgia there is however discordance between self-reported assessments and objective measurements of physical activity associated with catastrophizing cognitions [55]. Consequently, misleading information for this patient

population can be generated with physical activity questionnaires thus the use of objective measure, such as accelerometry, would be the preferred approach [56, 57].

Patients with fibromyalgia have been reported to have attenuated parasympathetic activity, assessed by heart rate variability, during non-REM stage 2 sleep and REM sleep which constituted about 80% of total sleep time [58]. The sympathetic autonomic nervous system is stimulated during physical activity, however after physical activity the sympathetic tone will decrease, and parasympathetic activity become dominant [59, 60]. The participation in physical activity will lead to the physiological responses of a decrease in heart rate and blood pressure with an anxiolytic effect which will facilitate better sleep quality. Non-restorative sleep associated with fibromyalgia may therefore be related to the altered autonomic nervous system (ANS) activity. Studies have demonstrated that aerobic and aquatic exercise, and resistance training, activities that modulate the ANS, have significantly decreased sleep disturbance and improved sleep quality in patients with fibromyalgia [61-63].

An association between pain severity and cognitive performance has been demonstrated which also appears to be influenced by sleep in individuals with fibromyalgia [64]. Thus, poor sleep quality is associated with pain severity and poor cognitive performance, and due to reciprocal relationships pain leads through an effect on sleep quality to impaired sustained attention [65]. Improved sleep quality would therefore offset the detrimental effects of pain on sustained attention. In addition to lower sustained attention, impaired performance speed in complex cognitive tasks is associated with low sleep quality in patients with fibromyalgia [66]. Intense pain experienced by patients with fibromyalgia have been associated with poor learning and memory performance, attention function and psychomotor processing speed [67-69].

4. Current Treatments for Fibromyalgia

Current treatment options of fibromyalgia focus on symptom-based management to improve quality of life with combination of pharmacological and non-pharmacological treatment to achieve the best outcome for the patient [1, 4]. Although the primary objective is often pain control, recommended treatment approaches of fibromyalgia produce some effect on sleep quality (Table 1). Treatments that improve sleep quality rather than quantity would decrease pain and fatigue whilst enhancing functioning and quality of life.

Table 1 Effect of pharmacological treatments on sleep disorder in fibromyalgia. FIQ fibromyalgia impact questionnaire, GABA gamma amino butyric acid.

Treatment	Class	Outcomes	Reference
Amitriptyline	Tricyclic antidepressant	Improved self-assessment of sleep quality using the FIQ scale	78
Cyclobenzaprine	Tricyclic muscle relaxant	Improved sleep quality, increased total sleep time, increased number of nights of restorative sleep.	82-86
Pregabalin	Gabapentanoid	Patients' report of improved sleep quality, decreased sleep	87-90

		latency and enhanced slow-wave sleep. Polysomnography recorded increase in sleep duration and slow wave sleep with a decrease in wake after sleep bouts.	
Gabapentin	Gabapentanoid	Improved sleep quantity and quality assessed by Medical Outcome Sleep Questionnaire.	91
Zolpidem	$GABA_A$ receptor agonist	Reduced time to fall asleep, increased sleep time, reduced awakenings and overall improvement in sleep.	93
Sodium Oxybate	Gamma-aminohydroxybutyrate and gamma-hydroxybutyrate receptor agonist	Facilitating slow-wave sleep and reducing wake periods after sleep onset.	96-99
Melatonin	Melatonergic receptor agonist	Decreased sleep latency and total nocturnal activity. Increased sleep efficiency, actual sleep time and assumed sleep.	109-114

4.1 Non-Pharmacological Treatments

As fibromyalgia is characterised with bad sleep hygiene and sleep fragmentation patients would benefit from behavioural interventions such as cognitive-behavioural therapy for sleep disturbance rather than pharmacological therapies focused to pain linked to sleep disruption. Cognitive behavioural therapy in patients with fibromyalgia improves subjective sleep, pain catastrophizing, anxiety and depression [70]. In a randomized controlled trial cognitive behavioural therapy for insomnia (CBT-I), involving sleep education and sleep hygiene training, and cognitive behavioural therapy for pain (CBT-P), involving pain education and adaptive techniques training, both led to improvements in self-reported sleep (wake after sleep onset, sleep efficiency, sleep quality) in patients with fibromyalgia [71]. The CBT-I achieved greater outcomes that persisted at 6 months. Interestingly neither treatment demonstrated improvement on objective sleep (actigraphy and polysomnography), pain or mood outcomes. Atrophy of cortical gray matter in regions such as the amygdala, anterior cingulate cortex, insula and thalamus has been reported in patients with fibromyalgia [72-74]. Individuals with fibromyalgia in an 8-week study receiving CBT-I demonstrated increases in cortical thickness following treatment and those receiving CBT-P showed less gray matter atrophy than untreated control subjects [75]. Thus, behavioural treatments for sleep disorder in fibromyalgia which demonstrated restorative benefit of consolidated sleep may be associated with cortical plasticity.

Balneotherapy has been used as a treatment in patients with fibromyalgia, with the passive immersion in hot baths (36 ^{o}C) benefiting pain and sleep quality [76]. In a study of sleep patterns

of patients with fibromyalgia using polysomnography, passive body heating decreased sleep onset time, REM sleep latency and the number of awakenings with improvement in sleep efficiency and slow wave sleep [77]. The likelihood that the reported effects are the result of passive body heating on sleep independent of the fibromyalgia cannot be ignored. As sleep disturbance can act as a trigger of fibromyalgia symptoms, passive body heating may thereby attenuate the expression of the condition.

4.2 Pharmacological Treatments

Antidepressant drugs, such as amitriptyline, duloxetine and milnacipran, are often used as a treatment of fibromyalgia [1, 4]. Low-dose amitriptyline (10-100 mg/day), a tricyclic antidepressant, has been shown to moderately improve pain, fatigue and sleep, with a lack of effect on mood [4, 78]. In contrast the serotonin and noradrenaline reuptake inhibitors, milnacipran (up to 200 mg/day) and duloxetine (up to 120 mg/day), failed to significantly improve parameters of sleep, studied by polysomnography, in patients with fibromyalgia [79-81]. Cyclobenzaprine, a tricyclic muscle relaxant chemically related to amitriptyline, (10 mg/day) has been reported to improve sleep quality, increase total sleep time and reduce pain in patients with fibromyalgia [82-85]. In a double-blind placebo-controlled study with very low-dose cyclobenzaprine (1-4 mg/day), polysomnography showed an increased number of nights of restorative sleep [86].

The gabapentanoids, pregabalin and gabapentin, exhibit efficacy as treatments of fibromyalgia [1, 4]. In randomised control trials with patients with fibromyalgia, pregabalin (300 and 450 mg/day) improved sleep quality based on patients' report with a decrease in sleep latency and enhancement of slow-wave sleep and reduced pain, anxiety and depression [87-89]. Polysomnography was used in a randomised placebo-controlled crossover trial to objectively study the effect of pregabalin (150-450 mg/day) on disturbed sleep in patients with fibromyalgia [90]. Sleep duration was significantly increased and wake after sleep bouts were significant decreased associated with slow wave sleep, consistent with pregabalin increasing deep sleep and improving sleep quality. Improved sleep quantity and quality assessed by Medical Outcome Sleep Questionnaire was observed during 12 weeks of an open-label study of gabapentin in patients with fibromyalgia [91].

The sedative hypnotics, zolpidem and zopiclone, enhance the inhibitory properties of GABA due to actions on $GABA_A$ receptors leading to increased slow wave sleep [92]. In double-blind randomized placebo-controlled trials of zolpidem (10 mg/day) patients with fibromyalgia demonstrated reduced time to fall asleep, increased sleep time, reduced awakenings and overall improvement in sleep [93]. In contrast zopiclone failed to modify self-assessed sleep architecture in patients with fibromyalgia, [94]. These medications are commonly prescribed for the treatment of insomnia, a complaint not characteristic of fibromyalgia where disturbed sleep with frequent awakening is typical in this patient group.

Sodium oxybate is an agonist of gamma-aminohydroxybutyrate and gamma-hydroxybutyrate receptors which is used in the treatment of excessive daytime sleepiness associated with narcolepsy [95]. In randomized placebo-controlled trials sodium oyxbate (4.5 or 6.0 g per night) reduced sleep disturbance by facilitating slow-wave sleep and reducing wake periods after sleep onset and reduced fatigue in patients with fibromyalgia [96-99]. Although there was a reduction in

pain this was not considered to be a direct effect, but a consequence of the improvements on sleep. These findings with sodium oxybate further support the sleep dysfunction in fibromyalgia having an important role in abnormal pain processing.

Melatonin is a neurohormone synthesized mainly by the pineal gland from tryptophan and serotonin that plays in a role in the regulation of the 24-hour pattern of bodily functions [100,101]. The symptoms of fibromyalgia being associated with dysregulation of the HPA and autonomic nervous systems has led to the proposal of involvement of melatonin and the melatonergic system in the pathophysiology of fibromyalgia. A decrease in melatonin synthesis due to low levels of tryptophan and serotonin as observed in patients with fibromyalgia may contribute to the characteristic symptoms of pain and abnormal sleeping patterns [2, 9]. Conflicting observations of the levels of melatonin in patients with fibromyalgia have however been reported with both abnormal levels and levels not different relative to health controls [102-108]. Interest from a potential therapeutic perspective as a treatment of fibromyalgia has been stimulated due to the chronotropic, analgesic and anxiolytic properties of melatonin. The therapeutic use of melatonin has been investigated in several studies of patients with fibromyalgia which included open-pilot, double-blind randomized controlled trial (RCT) and longitudinal placebo-controlled design [109-114]. In longitudinal placebo-controlled studies in patients with fibromyalgia, melatonin (6 – 15 mg/day) improved the symptoms related to sleep quality, fatigue and pain leading to enhanced quality of life [113, 114]. Objective sleep quality, assessed by actigraphy, and subjective sleep quality, assessed by the PSQI, was improved by 10 days of melatonin treatment (6 – 15 mg daily) to patients with fibromyalgia [114]. Administration of the higher doses of melatonin (12 and 15 mg daily) decreased sleep latency and total nocturnal activity, and increased sleep efficiency, actual sleep time and assumed sleep. Improvements in the symptoms of fibromyalgia in patients following melatonin administration are consistent with regulation of circadian rhythm synchronisation and a direct effect on pain pathways.

5. Conclusion

Non-restorative sleep associated with poor sleep quality is a characteristic of fibromyalgia which is linked to symptom severity. Biochemical abnormalities within the thalamus and related abnormal thalamic activity may be responsible for the sleep patterns in patients with fibromyalgia. Risk factors of fibromyalgia, including persistent pain, depression, cognitive performance, overweight and physical activity, appear to exhibit a reciprocal relationship with disordered sleep and could be predictors of subjective sleep quality. The observed association between disordered sleep and the risk of fibromyalgia suggests that the incidence of fibromyalgia would be reduced by limiting sleep problems. A relationship between sleep disorder and central sensitization could be a possible factor involved in development, exacerbation and/or maintenance of fibromyalgia [115].

These observations will provide clues for therapeutic approaches with treatments that consolidate or deepen sleep may be more preferential to improve sleep in patients with fibromyalgia in comparison to interventions whose primary mode of activity is to induce sleep. During the development of new treatments, polysomnography evidence demonstrating an effect on sleep architecturein patients with fibromyalgia is essential. The dosing regimes of drugs, tested as treatments of fibromyalgia, are often based on the pharmacokinetics adopted from use in the management of other conditions (e.g. anxiety, depression and epilepsy). Application of therapeutic

interventions more specific to fibromyalgia and the characteristic symptoms, including sleep disorder, may offer better effectiveness.

Thus, evidence is consistent with disordered sleep being fundamental to the pathophysiology of fibromyalgia and improvement of sleep quality can reduce other symptoms, such as pain, in individuals. The risk of sleep disturbances needs to be proactively assessed and when identified in this patient group be actively managed. Multidisciplinary interventions developed to manage, at least sleep quality and pain, would improve health outcomes for patients with fibromyalgia.

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Author Contributions

The author did all the research work of this study.

Competing Interests

The author declares no conflict of interest for the contributions in this manuscript.

References

1. Lawson K. Emerging pharmacological strategies for the treatment of fibromyalgia. World J Pharmacol. 2017: 6: 1-10.
2. Borchers AT, Gershwin ME. Fibromyalgia: A critical and comprehensive review. Clinic Rev Allerg Immunol. 2016; 49: 100-151.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum. 1990; 33: 160-172.
4. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017; 76: 318-328.
5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010; 62: 600-610.
6. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep. 2013; 17: 356.
7. Clauw DJ. Fibromyalgia: A clinical review. JAMA. 2014; 311: 1547-1555.
8. Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain. 2013; 136: 1857-1867.
9. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience. 2016; 338: 114-129.
10. Fayed N, Garcia-Campayo J, Magallón R, Andrés-Bergareche H, Luciano JV, Andres E, et al. Localized 1H-NMR spectroscopy in patients with fibromyalgia: A controlled study of changes in cerebral glutamate/glutamine, inositol, choline, and N-acetylaspartate. Arthritis Res Ther. 2010; 12: R134.

11. Pyke TL, Osmotherly PG, Baines S. Measuring glutamate levels in the brains of fibromyalgia patients and a potential role for glutamate in the pathophysiology of fibromyalgia symptoms: A systematic review. Clin J Pain. 2017; 33: 944-954.
12. Pimentel MJ, Gui MS, Reimão R, Rizzatti-Barbosa CM. Sleep quality and facial pain in fibromyalgia syndrome. Cranio. 2015; 33: 122-128.
13. Jacobson SA, Simpson RG, Lubahn C, Hu C, Belden CM, Davis KJ, et al. Characterization of fibromyalgia symptoms in patients 55-95 years old: A longitudinal study showing symptom persistence with suboptimal treatment. Aging Clin Exp Res. 2015; 27: 75-82.
14. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord. 2007; 8: 27.
15. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: Longitudinal data on an adult female population in Norway. Arthritis Rheum. 2012; 64: 281-284.
16. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. Arthritis Rheum. 2001; 44: 222-230.
17. Viola-Saltzman M, Watson NF, Bogart A, Goldberg J, Buchwald D. High prevalence of restless legs syndrome among patients with fibromyalgia: A controlled cross-sectional study. J Clin Sleep Med. 2010; 6: 423-427.
18. Moldofsky H. Sleep and fibrositis syndrome. Rheum Dis Clin North Am. 1989; 15: 91-103.
19. Garip Y, Öztaş D, Güler T. Prevalence of fibromyalgia in Turkish geriatric population and its impact on quality of life. Agri. 2016; 28: 165-170.
20. Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci. 1998; 315: 367-376.
21. Diaz-Piedra C, Catena A, Sánchez AI, Miró E, Martínez MP, Buela-Casal G. Sleep disturbances in fibromyalgia syndrome: The role of clinical and polysomnographic variables explaining poor sleep quality in patients. Sleep Med. 2015; 16: 917-925.
22. Wu YL, Chang LY, Lee HC, Fang SC, Tsai PS. Sleep disturbances in fibromyalgia: A meta-analysis of case-control studies. J Psychosom Res. 2017; 96: 89-97.
23. Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol. 1999; 26: 1586-1592.
24. Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM. Hypothalamic-pituitary-insulin-like growth factor-I axis dysfunction in patients with fibromyalgia. J Rheumatol. 1997; 24: 1384-1389.
25. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. Arthritis Rheum. 1992; 35: 1113-1116.
26. Culebras A, Miller M. Dissociated patterns of nocturnal prolactin, cortisol, and growth hormone secretion after stroke. Neurology. 1984; 34: 631-636.
27. Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, et al. Regional cerebral blood flow in fibromyalgia: Single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthritis Rheum. 2000; 43: 2823-2833.
28. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol. 2004; 31: 364-378.

29. Okifuji A, Hare BD. Nightly analyses of subjective and objective (actigraphy) measures of sleep in fibromyalgia syndrome: What accounts for the discrepancy? Clin J Pain. 2011; 27: 289-296.
30. Çetin B, Güleç H, Toktaş HE, Ulutaş Ö, Yılmaz SG, İsbir T. Objective measures of sleep in fibromyalgia syndrome: Relationship to clinical, psychiatric, and immunological variables. Psychiatry Res. 2018; 263: 125-129.
31. Skarpsno ES, Nilsen TIL, Sand T, Hagen K, Mork PJ. Do physical activity and body mass index modify the association between chronic musculoskeletal pain and insomnia? Longitudinal data from the HUNT study, Norway. J Sleep Res. 2018; 27: 32-39.
32. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: An update and a path forward. J Pain. 2013; 14: 1539-1552.
33. Theadom A, Cropley M, Humphrey KL. Exploring the role of sleep and coping in quality of life in fibromyalgia. J Psychosom Res. 2007; 62: 145-151.
34. Theadom A, Cropley M, Kantermann T. Daytime napping associated with increased symptom severity in fibromyalgia syndrome. BMC Musculoskelet Disord. 2015; 16: 13.
35. Sivertsen B, Lallukka T, Salo P, Pallesen S, Hysing M, Krokstad S, et al. Insomnia as a risk factor for ill health: Results from the large population-based prospective HUNT Study in Norway. J Sleep Res. 2014; 23: 124-132.
36. McBeth J, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults: Results from a population-based prospective cohort study in the UK. Arthritis Rheumatol. 2014; 66: 757-767.
37. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep. 2006; 29: 145-151.
38. Korszun A, Young EA, Engleberg NC, Brucksch CB, Greden JF, Crofford LA. Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. J Psychosom Res. 2002; 52: 439-443.
39. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: Relationship to pain and depression. Arthritis Rheum. 2008; 59: 961-967.
40. Hall M, Buysse DJ, Nowell PD, Nofzinger EA, Houck P, Reynolds CF 3rd, et al. Symptoms of stress and depression as correlates of sleep in primary insomnia. Psychosom Med. 2000; 62: 227-230.
41. Kim CH, Luedtke CA, Vincent A, Thompson JM, Oh TH. Association of body mass index with symptom severity and quality of life in patients with fibromyalgia. Arthritis Care Res (Hoboken). 2012; 64: 222-228.
42. Okifuji A, Donaldson GW, Barck L, Fine PG. Relationship between fibromyalgia and obesity in pain, function, mood, and sleep. J Pain. 2010; 11: 1329-1337.
43. May KP, West SG, Baker MR, Everett DW. Sleep apnea in male patients with the fibromyalgia syndrome. Am J Med. 1993; 94: 505-508.
44. Gold AR, Dipalo F, Gold MS, Broderick J. Inspiratory airflow dynamics during sleep in women with fibromyalgia. Sleep. 2004; 27: 459-466.
45. Rosenfeld VW, Rutledge DN, Stern JM. Polysomnography with quantitative EEG in patients with and without fibromyalgia. J Clin Neurophysiol. 2015; 32: 164-170.

46. Mork PJ, Vasseljen O, Nilsen TI. Association between physical exercise, body mass index, and risk of fibromyalgia: Longitudinal data from the Norwegian Nord-Trøndelag Health Study. Arthritis Care Res (Hoboken). 2010; 62: 611-617.
47. Shapiro JR, Anderson DA, Danoff-Burg S. A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. J Psychosom Res. 2005; 59: 275-282.
48. Saber AA, Boros MJ, Mancl T, Elgamal MH, Song S, Wisadrattanapong T. The effect of laparoscopic Roux-en-Y gastric bypass on fibromyalgia. Obes Surg. 2008; 18: 652-655.
49. Marvisi M, Balzarini L, Mancini C, Ramponi S, Marvisi C. Fibromyalgia is frequent in obstructive sleep apnea and responds to CPAP therapy. Eur J Intern Med. 2015; 26: e49-e50.
50. Skarpsno ES, Nilsen TIL, Sand T, Hagen K, Mork PJ. The joint effect of insomnia symptoms and lifestyle factors on risk of self-reported fibromyalgia in women: Longitudinal data from the HUNT Study. BMJ Open. 2019; 9: e028684.
51. Munguía-Izquierdo D, Legaz-Arrese A. Determinants of sleep quality in middle-aged women with fibromyalgia syndrome. J Sleep Res. 2012; 21: 73-79.
52. Segura-Jiménez V, Álvarez-Gallardo IC, Estévez-López F, Soriano-Maldonado A, Delgado-Fernández M, Ortega FB, et al. Differences in sedentary time and physical activity between female patients with fibromyalgia and healthy controls: The al-Ándalus project. Arthritis Rheumatol. 2015; 67: 3047-3057.
53. Segura-Jiménez V, Borges-Cosic M, Soriano-Maldonado A, Estévez-López F, Álvarez-Gallardo IC, Herrador-Colmenero M, et al. Association of sedentary time and physical activity with pain, fatigue, and impact of fibromyalgia: The al-Ándalus study. Scand J Med Sci Sports. 2017; 27: 83-92.
54. Borges-Cosic M, Aparicio VA, Estévez-López F, Soriano-Maldonado A, Acosta-Manzano P, Gavilán-Carrera B, et al. Sedentary time, physical activity, and sleep quality in fibromyalgia: The al-Ándalus project. Scand J Med Sci Sports. 2019; 29: 266-274.
55. Estévez-López F, Álvarez-Gallardo IC, Segura-Jiménez V, Soriano-Maldonado A, Borges-Cosic M, Pulido-Martos M, et al. The discordance between subjectively and objectively measured physical function in women with fibromyalgia: Association with catastrophizing and self-efficacy cognitions. The al-Ándalus project. Disabil Rehabil. 2018; 40: 329-337.
56. Segura-Jiménez V, Alvarez-Gallardo IC, Romero-Zurita A, Camiletti-Moirón D, Munguía-Izquierdo D, Carbonell-Baeza A, et al. Comparison of physical activity using questionnaires (leisure time physical activity instrument and physical activity at home and work instrument) and accelerometry in fibromyalgia patients: The Al-Ándalus project. Arch Phys Med Rehabil. 2014; 95: 1903-1911.
57. Freedson P, Bowles HR, Troiano R, Haskell W. Assessment of physical activity using wearable monitors: Recommendations for monitor calibration and use in the field. Med Sci Sports Exerc. 2012; 44: S1-S4.
58. Mork PJ, Nilsson J, Lorås HW, Riva R, Lundberg U, Westgaard RH. Heart rate variability in fibromyalgia patients and healthy controls during non-REM and REM sleep: A case-control study. Scand J Rheumatol. 2013; 42: 505-508.
59. O'Connor PJ, Youngstedt SD. Influence of exercise on human sleep. Exerc Sport Sci Rev. 1995; 23: 105-134.
60. Kubitz KA, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. Sports Med. 1996; 21: 277-291.

61. Munguía-Izquierdo D, Legaz-Arrese A. Assessment of the effects of aquatic therapy on global symptomatology in patients with fibromyalgia syndrome: A randomized controlled trial. Arch Phys Med Rehabil. 2008; 89: 2250-2257.
62. Andrade A, Vilarino GT, Bevilacqua GG. What is the effect of strength training on pain and sleep in patients with fibromyalgia? Am J Phys Med Rehabil. 2017; 96: 889-893.
63. Bircan C, Karasel SA, Akgün B, El O, Alper S. Effects of muscle strengthening versus aerobic exercise program in fibromyalgia. Rheumatol Int. 2008; 28: 527-532.
64. Dick BD, Verrier MJ, Harker KT, Rashiq S. Disruption of cognitive function in fibromyalgia syndrome. Pain. 2008; 139: 610-616.
65. Fang SC, Wu YL, Chen SC, Teng HW, Tsai PS. Subjective sleep quality as a mediator in the relationship between pain severity and sustained attention performance in patients with fibromyalgia. J Sleep Res. 2019; 28: e12843.
66. C-oté KA, Moldofsky H. Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. J Rheumatol. 1997; 24: 2014-2023.
67. Wu YL, Huang CJ, Fang SC, Ko LH, Tsai PS. Cognitive impairment in fibromyalgia: A meta-analysis of case-control studies. Psychosom Med. 2018; 80: 432-438.
68. Galvez-Sánchez CM, Reyes Del Paso GA, Duschek S. Cognitive impairments in fibromyalgia syndrome: Associations with positive and negative affect, alexithymia, pain catastrophizing and self-esteem. Front Psychol. 2018; 9: 377.
69. Veldhuijzen DS, Sondaal SF, Oosterman JM. Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed. J Pain. 2012; 13: 507-515.
70. Martínez MP, Miró E, Sánchez AI, Díaz-Piedra C, Cáliz R, Vlaeyen JW, et al. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: A randomized controlled trial. J Behav Med. 2014; 37: 683-697.
71. McCrae CS, Williams J, Roditi D, Anderson R, Mundt JM, Miller MB, et al. Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: Clinical outcomes from the SPIN randomized controlled trial. Sleep. 2019; 42: zsy234.
72. Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R. Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. J Pain. 2011; 12: 436-443.
73. Lutz J, Jäger L, de Quervain D, Krauseneck T, Padberg F, Wichnalek M, et al. White and gray matter abnormalities in the brain of patients with fibromyalgia: A diffusion-tensor and volumetric imaging study. Arthritis Rheum. 2008; 58: 3960-3969.
74. Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. Psychosom Med. 2009; 71: 566-573.
75. McCrae CS, Mundt JM, Curtis AF, Craggs JG, O'Shea AM, Staud R, et al. Gray matter changes following cognitive behavioral therapy for patients with comorbid fibromyalgia and insomnia: A pilot study. J Clin Sleep Med. 2018; 14: 1595-1603.
76. Langhorst J, Musial F, Klose P, Häuser W. Efficacy of hydrotherapy in fibromyalgia syndrome-a meta-analysis of randomized controlled clinical trials. Rheumatology (Oxford). 2009; 48: 1155-1159.
77. Silva A, Queiroz SS, Andersen ML, Mônico-Neto M, Campos RM, Roizenblatt S, et al. Passive body heating improves sleep patterns in female patients with fibromyalgia. Clinics (Sao Paulo). 2013; 68: 135-140.

78. Lawson K. A Brief Review of the Pharmacology of amitriptyline and clinical outcomes in treating fibromyalgia. Biomedicines. 2017; 5: E24.
79. Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: Secondary analysis of a randomized, placebo-controlled trial. Arthritis Res Ther. 2011; 13: R86.
80. Ahmed M, Aamir R, Jishi Z, Scharf MB. The effects of milnacipran on sleep disturbance in fibromyalgia: A randomized, double-blind, placebo-controlled, two-way crossover study. J Clin Sleep Med. 2016; 12: 79-86.
81. Häuser W, Petzke F, Üçeyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: A systematic review with meta-analysis. Rheumatology (Oxford). 2011; 50: 532-543.
82. Bennett RM, Gatter RA, Campbell SM, Andrews RP, Clark SR, Scarola JA. A comparison of cyclobenzaprine and placebo in the management of fibrositis. A double-blind controlled study. Arthritis Rheum. 1988; 31: 1535-1542.
83. Quimby LG, Gratwick GM, Whitney CD, Block SR. A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. J Rheumatol Suppl. 1989; 19: 140-143.
84. Reynolds WJ, Moldofsky H, Saskin P, Lue FA. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. J Rheumatol. 1991; 18: 452-454.
85. Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum. 1994; 37: 32-40.
86. Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: A double-blind randomized placebo-controlled study. J Rheumatol. 2011; 38: 2653-2663.
87. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep. 2005; 28: 187-193.
88. Arnold LM, Emir B, Pauer L, Resnick M, Clair A. Time to improvement of pain and sleep quality in clinical trials of pregabalin for the treatment of fibromyalgia. Pain Med. 2015; 16: 176-185.
89. Arnold LM, Sarzi-Puttini P, Arsenault P, Khan T, Bhadra Brown P, Clair A, et al. Efficacy and safety of pregabalin in patients with fibromyalgia and comorbid depression taking concurrent antidepressant medication: A randomized, placebo-controlled study. J Rheumatol. 2015; 42: 1237-1244.
90. Roth T, Bhadra-Brown P, Pitman VW, Resnick EM. Pregabalin improves fibromyalgia-related sleep disturbance. Clin J Pain. 2016; 32: 308-312.
91. North JM, Hong KS, Rauck RL. The effect of a novel form of extended-release gabapentin on pain and sleep in fibromyalgia subjects: An open-label pilot study. Pain Pract. 2016; 16: 720-729.
92. Lancel M. Role of GABAA receptors in the regulation of sleep: Initial sleep responses to peripherally administered modulators and agonists. Sleep. 1999; 22: 33-42.

93. Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds WJ. The effect of zolpidem in patients with fibromyalgia: A dose ranging, double blind, placebo controlled, modified crossover study. J Rheumatol. 1996; 23: 529-533.
94. Grönblad M, Nykänen J, Konttinen Y, Järvinen E, Helve T. Effect of zopiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial. Clin Rheumatol. 1993; 12: 186-191.
95. Mamelak M, Black J, Montplaisir J, Ristanovic R. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. Sleep. 2004; 27: 1327-1334.
96. Russell IJ, Perkins AT, Michalek JE. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: A randomized, double-blind, placebo-controlled, multicenter clinical trial. Arthritis Rheum. 2009; 60: 299-309.
97. Moldofsky H, Inhaber NH, Guinta DR, Alvarez-Horine SB. Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: A double-blind, randomized, placebo-controlled study. J Rheumatol. 2010; 37: 2156-2166.
98. Russell IJ, Holman AJ, Swick TJ, Alvarez-Horine S, Wang YG, Guinta D. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: Results from a 14-week, randomized, double-blind, placebo-controlled study. Pain. 2011; 152: 1007-1017.
99. Spaeth M, Bennett RM, Benson BA, Wang YG, Lai C, Choy EH. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: Results of an international phase 3 trial. Ann Rheum Dis. 2012; 71: 935-942.
100. Vanecek J. Cellular mechanisms of melatonin action. Physiol Rev. 1998; 78: 687-721.
101. Hardeland R, Cardinali DP, Srinivasan V Spence DW, Brown GM, Pandi-Perumal SR. Melatonin – a pleiotropic, orchestrating regulator molecule. Prog Neurobiol. 2011; 93: 350-384.
102. Wikner J, Hirsch U, Wetterberg L, Röjdmark S. Fibromyalgia--a syndrome associated with decreased nocturnal melatonin secretion. Clin Endocrinol (Oxf). 1998; 49: 179-183.
103. Press J, Phillip M, Neumann L, Barak R, Segev Y, Abu-Shakra M, et al. Normal melatonin levels in patients with fibromyalgia syndrome. J Rheumatol. 1998; 25: 551-555.
104. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999; 26: 2675-2680.
105. Klerman EB, Goldenberg DL, Brown EN, Maliszewski AM, Adler GK. Circadian rhythms of women with fibromyalgia. J Clin Endocrinol Metab. 2001; 86: 1034-1039.
106. Senel K, Baygutalp F, Baykal T, Erdal A, Ugur M. Melatonin levels in premenopausal women with fibromyalgia syndrome. Rheumatol Int. 2013; 33: 1609-1610.
107. Pernambuco AP, Schetino LP, Viana RS, Carvalho LS, d'Ávila Reis D. The involvement of melatonin in the clinical status of patients with fibromyalgia syndrome. Clin Exp Rheumatol. 2015; 33: S14-S19.
108. Caumo W, Hidalgo MP, Souza A, Torres ILS, Antunes LC. Melatonin is a biomarker of circadian dysregulation and is correlated with major depression and fibromyalgia symptom severity. J Pain Res. 2019; 12: 545-556.

109. Citera G, Arias MA, Maldonado-Cocco JA, Lázaro MA, Rosemffet MG, Brusco LI, et al. The effect of melatonin in patients with fibromyalgia: A pilot study. Clin Rheumatol. 2000; 19: 9-13.
110. Acuna-Castroviejo D, Escames G, Reiter RJ. Melatonin therapy in fibromyalgia. J Pineal Res. 2006; 40: 98-99.
111. Hussain SA, Al-Khalifa II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. J Pineal Res. 2011; 50: 267-271.
112. de Zanette SA, Vercelino R, Laste G, Laste G, Rozisky JR, Schwertner A. et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: A phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014; 15: 40.
113. Castaño MY, Garrido M, Delgado-Adamez J, Gómez MÁ. Oral melatonin administration improves the objective and subjective sleep quality, increases 6-sulfatoxymelatonin levels and total antioxidant capacity in patients with fibromyalgia. J Appl Biomed. 2018; 16: 186-191.
114. Castaño MY, Garrido M, Rodríguez AB, Gómez MÁ. Melatonin improves mood status and quality of life and decreases cortisol levels in fibromyalgia. Biol Res Nurs. 2019; 21: 22-29.
115. Nijs J, Loggia ML, Polli A, Moens M, Huysmans E, Goudman L, et al. Sleep disturbances and severe stress as glial activators: Key targets for treating central sensitization in chronic pain patients? Expert Opin Ther Targets. 2017; 21: 817-826.