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Sleep Disorders in Fibromyalgia Syndrome

Maurizio Rizzi[1*], Andrea Cristiano[1], Francesca Frassanito[1], Claudio Macaluso[1], Andrea Airoldi[1] and Piercarlo Sarzi-Puttini[2]

[1]Respiratory Unit, Center for Sleep and Respiratory Disorders "Luigi Sacco" University Hospital, Milan, Italy
[2]Rheumatology Unit, "Luigi Sacco" University Hospital, Milan, Italy

Abstract

Chronic pain in patients affected by fibromyalgia is nowadays considered as a result of dysregulated mechanisms in the central nervous system. As fibromyalgia patients often report sleep disturbances, some researches have investigated potential central neural dysfunctions which link chronic pain and alterations responsible for sleep disorders. Polysomnography in fibromyalgia patients reveals increased EEG alpha activity during non REM sleep, increased number of arousal and a more frequent occurrence of cyclic alternating pattern.

Mechanisms potentially linking chronic widespread pain to sleep alterations and mood disorders have not been proved. The relationship between polysomnographic findings and clinical symptoms in patients with fibromyalgia supports the hypothesis of a conceptual common mechanism called central sensation.

The first step in the therapeutic approach is sleep assessment, including sleep history, identification of factors interfering with sleep hygiene and the diagnosis of any underlying disorder that may affect sleep.

Food and Drug Administration has approved drugs for fibromyalgia that can improve sleep quality, but not specific for treatment of fibromyalgia associated sleep disorders.

Both pharmacological and non pharmacological treatments should be used cautiously in fibromyalgia patients, considering underlying disorders and their potential interactions. However they could be an effective treatment both for fibromyalgia related pain and coexisting sleep alteration.

Keywords: Fibromyalgia; Sleep disorders; Chronic pain

Introduction

Fibromyalgia (FM) is a chronic pain disorder of unknown aetiology characterized by diffuse musculoskeletal pain and increased tenderness at palpation.

More progress in understanding FM and its related syndromes was made when investigators turned their attention to the role played by the nervous system [1,2].

A large percentage of FM patients report sleep disturbance, including difficulties in falling or staying asleep, early morning awakenings and non-restorative sleep [3-5].

Sleep is a regular circadian phase of reduced activity and responsiveness, with characteristic physiologic changes, especially in the brain [6]. The cyclicity of sleep is linked to other biologic circadian rhythms, such as hormone secretion (e.g., growth hormone, prolactin, and melatonin), body temperature and blood pressure [7].

Research about sleep disorders in patients with chronic pain, particularly in FM patients, overlaps the concept of non restorative sleep. The restorative theory considers brain activity during sleep essential to restore body and mind [8,9]. As non restorative sleep is common in patients with organic sleep disorders, it has been considered a symptom of insomnia. Many studies have investigated the symptoms of insomnia associated with chronic pain syndromes, particularly FM and chronic pain fatigue syndrome, but there are few studies about non restorative sleep: a greater knowledge of non restorative sleep and its mechanisms could provide important insights into the causes of FM and related condition.

Poor sleep quality or quantity increases the risk of medical and psychiatric diseases [10,11].

The current method of assessing physiological sleep parameters is based on polysomnography (PSG), which records muscle tone through an electromyography (EMG), eye movements through electrooculography, and brain activity by means of electroencephalography (EEG). The two main stages of sleep are rapid eye movement (REM) sleep, which is believed to be important for processing and memory consolidation of cognitive stimuli encountered while awake [12], and non-REM sleep, which the American Academy of Sleep Medicine classification currently divides into three stages (N1, N2 and N3), although previously there were four stages [13]. Stage W (wakefulness), during which the predominant EEG findings are alpha waves with a frequency of 8-12 Hz; stage N1 (light sleep, normally <5% of total sleep time), during which the main EEG findings are theta waves with a frequency of 4–7 Hz (this stage of true sleep is characterised by slow and regular eye movements); stage N2 (intermediate sleep, 40–50% of total sleep time), deeper sleep characterised by EEG findings of sleep spindles and K complex, with no slow and regular eye movements; and stage N3 (deep or slow wave sleep, 20% of total sleep time), characterised by EEG findings of slow delta waves with a frequency of 0.5–2 Hz.

During the first half of sleep, individual's cycle between REM and all stages of non REM sleep; during the second half, the cycling is between stage N2 and REM sleep. Each cycle normally lasts 1–2 hours whereas stage N1 typically lasts <30 minutes.

Aetiology

There are many prospective clinical studies demonstrating a

***Corresponding author:** Maurizio Rizzi, Ospedale "Luigi Sacco" Azienda Ospedaliera, Polo Universitario, Via GB Grassi, 74, 20157, Milano, Italy, Tel: 390239042777; Fax: 390239042613; E-mail: rizzi.maurizio@hsacco.it

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correlation between FM symptoms and poor sleep quality. One statistical path analysis shows that the greater sleep disorder is, the worse pain and physical functioning are, which in turn predicts greater depression [14]. Another study shows that a night of poorer sleep is followed by a more painful day, whereas sleep quality was not explained by changes in pain intensity during the day [15]. It was found that, after adjusting for the effects of pain and negative and positive events on daily affective scores, sleep quality and duration were prospectively related to fatigue and affect. Inadequate sleep has a cumulative effect on negative affects and prevented affective recovery from days with a high number of negative events [16].

Onen et al. [17] in a study based on total sleep deprivation or specific deprivation of slow wave sleep (SWS) or REM sleep confirmed the existence of alterations in pain measures in normal subjects. In one of these, a total of 40 hours sleep deprivation reduced pain threshold, which returned to baseline values after a period of undisturbed sleep, possibly because of the restoration of SWS.

Its was reported that FM patients complaining for daytime hypersomnolence had a higher number of tender points, a greater score of subjective pain and more fatigue than FM patients with no daytime hypersomnolence [18]. It has also been shown that the experimentally induced disruption of deep SWS can increase symptoms of pain [19-21].

The causal relationships between FM and sleep are not clear. There are probably neuroendocrine or genetic triggers inducing pain, sleep and mood mechanisms: for example serotonin abnormalities may play a role in FM and the related sleep and mood disorders [22].

Epidemiology and symptoms

Patients affected by FM are generally aware of the bad quality of their sleep [23]. They often describe their sleep as non restorative and to wake up many times during the night. They often refer pain and stiffness even during night time and in the morning; they feel unrefreshed and poorly satisfied with their sleep [24].

Sleep studies suggested that 75–90% of FM patients report non restorative sleep [25]. Bengtsson et al. [26] for example reported that 53% of FM patients experience difficulties falling asleep, 71% report frequent awakening at night and 78% were not satisfied with their own sleep.

An internet survey of more than 2500 FM USA patients reported morning stiffness, fatigue, non restorative sleep, pain, concentration and memory problems as the most severe symptoms [27]. A study of almost 700 FM patients showed that chronic widespread pain and non restorative sleep were key symptoms [28].

It is clear that unrefreshing or non restorative sleep is directly related to pain and fatigue as the most common symptoms of FM patients. In 2009 the OMERACT (originally Outcome Measures in Rheumatoid Arthritis Clinical Trials, but now Outcome Measures in Rheumatology) group understood that FM is a multisymptom syndrome and included fatigue and sleep disturbance in the inner core set of disease domains to be assessed in all clinical trials of FM [29].

Alteration of sleep architecture

Different studies regarding sleep architecture in FM patients have been conducted since the first report by Moldofsky [19] in which it is shown that the experimental disruption of SWS induced musculoskeletal pain and fatigue symptom in healthy sleeping subjects. Numerous studies identified alpha activity in non REM stages in adults and children with FM, as well as in individuals with chronic fatigue syndrome [30-33]. It was also hypothesised that EEG alpha activity could be a sleep maintaining or a sleep disrupting factor depending on which part of the brain it comes from Pivik et al. [34]. Several polysomnographic studies of FM patients found disordered sleep architecture with the delayed onset of EEG sleep [32,35], poorer sleep efficiency [17,24] and reduced SWS and REM sleep [24,32,35,36].

The presence of wave alpha intrusion in non REM sleep is not always found in FM patients. It is common in several health problems in which unrefreshing sleep is presumably related to this anomaly and it doesn't seem to be specific for FM syndrome [4]. The EEG alpha disorders indicate a vigilant state during non REM sleep leading to daytime symptoms [31] but Chervin et al. [37] in a small-scale study on the presence of EEG alpha during SWS did not mention the anomaly.

Some studies showed a reduction in stage N2 sleep spindles and in stage N2 sleep periods [38,39]. Another study found a high frequency of cyclic alternating pattern (CAP) [40], which is a periodic EEG sleep phenomenon that provides physiological measure of sleep stability. The CAP phase A1 pattern is an index of sleep stability, whereas CAP phase A2 and A3 are markers of progressive sleep instability or poor sleep quality. Increases in these last two patterns were found in FM patients with poor sleep quality associated with disease severity [40].

Abnormalities of circadian rhythm and biochemical alteration

Disturbances of body circadian rhythm can contribute to poor sleep, fatigue and exacerbations of other symptoms of FM [41]. In humans circadian rhytmicity is originated by hypothalamus and FM patients have a disturbed hypothalamic cortical adrenal axis [42,43]. Many studies show that FM patients have decreased levels of growth hormone (GH) [44,45] and its metabolites, particularly during the night [46].

Moutz et al. [47] used neuro-imaging of FM patients to examine regional cerebral blood flow (rCBF) to specific brain structures and showed that rCBF to the thalamus and caudate nucleus was decreased in FM patients. Moreover, the loss GH secretion during slow wave sleep may be linked to lesions in dorsal medial nucleus of the thalamus [48] suggesting that rCBF may be involved in the GH secretion abnormalities observed in FM patients.

Frequent alpha wave intrusion during delta wave sleep has been associated with the reduced production of GH and insuline-like growth factor 1 (IGF1) [49,50]. Moreover GH and IGF1 are involved in the repair of muscle micro traumas. Sleep disturbances may affect physiological healing mechanisms after muscle-tissue damage. This may alter the transmission of sensory stimuli from damaged muscle tissue to nervous system and enhance the perception of muscle pain [51]. About 90% of FM patients had inadequate GH response to exercise [45] and one-third significantly low circulating IGF-1 levels [51].

GH replacement therapy significantly improved symptoms and reduced the number of tender points in FM patients [52].

Elevated cerebral spinal fluid levels of substance P were also found in patients with FM [53]. Substance P, a neuractive peptide, is widely distributed throughout the nervous system and may contribute to arousal [54]. Experimental studies showed that substance P influences nociception and sleep via a neurokinin pathway [55].

These findings seem to support the hypothesis that a decrease in substance P levels may reduce the arousing effects of substance P on the

sleep/waking brain function in FM patients.

Sleep treatment approach

Poor sleep is one of the main symptoms in FM patients and could be due or exacerbated by a variety of factors. It is important, before starting to use a pharmacological approach, to obtain a detailed history that includes not only the patient's sleep habits but also his life style. It is therefore useful to evaluate whether or not the patient is suffering from sleep disturbances such sleep apnoea or restless leg syndrome and define the environmental conditions during sleep (noisy ambient, snoring partner, children etc.); by accurately collecting these data, it's possible to correct a life style which, sometimes, may contribute to alter the quality of sleep in FM patients.

Here are some advices for patients in order to improve the quality of their sleep:

- to maintain a regular sleep-waking rhythm every day;
- to sleep an appropriate number of hours (at least 6 hours per night);
- to perform daily moderate physical activity;
- to avoid foods and/or pharmacological substance which may interfere with sleep (smoke, alcohol, drugs, cocaine);
- To sleep in a quiet room with constant temperature, without noise or troublesome light sources.

Some non-pharmacological physical methods such as ultrasound and interferential current treatments, may increase slow wave sleep and decrease the percentage of N1 sleep stage [56], reduce the periods of unrefreshing sleep, fatigue, pain and the number of tender points. Transcranial direct current stimulation of the primary motor cortex may decrease arousals, thus reducing pain and increasing sleep quality and efficiency [57].

U.S. Food and Drug Administration and the European Medicines Agency approved three medications for FM: pregabalin, duloxetine and milnacipram. It is demonstrated that all these medications can positively influence sleep [58-62]. Duloxetine and milnacipram delay the onset and reduce the duration of REM sleep, improving sleep continuity and quality [63]. Pregabalin has beneficial effects on pain, fatigue and quality of sleep [58]. Sleep improvement could be direct or due to the reduction in pain or both [59,62,64].

FM patients are often treated with drugs that are not formally approved for this indication, and some of these may also improve FM related sleep disturbances. These include tricyclic antidepressants, other antidepressants and anticonvulsants.

Neither cyclobenzaprine nor amitryptiline seem to alter alpha non REM sleep. A small scale study of cyclobenzaprine found a beneficial effect on pain and no occurrence of EEG alpha sleep disorders; furthermore 10–50 mg decreased evening fatigue and increased total sleep time [60].

Amitriptyline treatment showed that a small proportion of FM patients was affected by alpha non REM sleep anomaly, although the effect was not statistically significant. Clinical experience showed that traditional sedatives and hypnotic benzodiazepine do not lead to any specific benefit [65,66].

Sodium Oxybate is a sleep promoting drug that may have beneficial effects on sleep physiology, restorative sleep, pain and fatigue. It is a metabolite of the inhibitor neurotransmitter gamma-aminobutyne acid, and its highest concentration is found in the hypothalamus and basal ganglia.

In FM patients it promotes the normalization of non REM sleep and increases slow wave sleep, thus improving the quality of sleep [67]

Conclusion

In 2010 the American College of Rheumatology in Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity [68] included patient-reported measure of unrefreshing sleep (assessed by means of visual analogue scales) to support a diagnosis of FM. Since managing sleep disorders could reduce FM symptoms, it seems reasonable to include an evaluation of sleep problems in the examination of FM patients [64,69]. Other disorders that may influence sleep should be ruled out (sleep apnoea syndrome, periodic limb movement), as well as any other medical condition that may be associated with sleep disorders (diabetes, thyroid disorders, hypertension). The principles underlying the evaluation of sleep and sleep disorders are described in detail elsewhere [70]. Correcting sleep disorders could reduce the symptoms severity and improve quality of life in FM patients.

There is still a lack of studies involving the routine PSG testing for FM patients [71], but PSG should be used if a detailed sleep history and related examination suggest an underlying primary sleep abnormality.

References

1. Yunus MB (1992) Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation. J Rheumatol 19: 846-850.
2. Clauw DJ, Chrousos GP (1997) Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 4: 134-153.
3. Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, et al. (2007) Fibromyalgia syndrome. J Rheumatol 34: 1415-1425.
4. Moldofsky H (2008) The significance of the sleeping-wakening brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. Joint Bone Spine 75: 397-402.
5. Stuifbergen AK, Phillips I, Carter P, Morrison J, Todd A (2010) Subjective and objective sleep difficulties in women with fibromyalgia syndrome. Journal of American Academy of Nurse Practitioners 22: 548-556.
6. Kryger MH, Roth T, Carskadon M (2005) Circadian rhythms in humans: an overview. In Principles and practice of sleep medicine. Philadelphia W.B. Saunders 301-308.
7. Crofford LJ (1998) Neuroendocrine abnormalities in fibromyalgia and related disorders. Am J Med Sci 315: 359-366.
8. Adam K, Oswald I (1983) Protein synthesis, bodily renewal and the sleep-wake cycle. Clin Sci (Lond) 65: 561-567.
9. Shapiro CM, Bortz R, Mitchell D, Bartel P, Jooste P (1981) Slow-wave sleep: a recovery period after exercise. Science 214: 1253-1254.
10. Krystal AD (2006) Sleep and psychiatric disorders: future directions. Psychiatr Clin North Am 29: 1115-1130.
11. Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, et al. (2010) Sleep symptoms predict the development of the metabolic syndrome. Sleep 33: 1633-1640.
12. Nishida M, Pearsall J, Buckner RL, Walker MP (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19: 1158-1166.
13. Jafari B, Mohsenin V (2010) Polysomnography. Clin Chest Med 31: 287-297.
14. Bigatti SM, Hernandez AM, Cronan TA, Rand KL (2008) Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Rheum 59: 961-967.
15. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M (1996) Sequential daily

relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain 68: 363-368.

16. Hamilton NA, Affleck G, Tennen H, Karlson C, Luxton D, et al. (2008) Fibromyalgia: the role of sleep in affect and in negative event reactivity and recovery. Health Psychol 27: 490-497.
17. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C (2001) The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subject. Journal of sleep research 10: 35-42.
18. Sarzi-Puttini P, Rizzi M, Andreoli A, Panni B, Pecis M, et al. (2002) Hypersomnolence in fibromyalgia syndrome. Clin Exp Rheumatol 20: 69-72.
19. Moldofsky H, Scarisbrick P, England R, Smythe H (1975) Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 37: 341-351.
20. Moldofsky H, Scarisbrick P (1976) Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med 38: 35-44.
21. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T (2006) Sleep loss and REM sleep loss are hyperalgesic. Sleep 29: 145-151.
22. Arnold LM, Clauw DJ (2010) Fibromyalgia syndrome: practical strategies for improving diagnosis and patient outcomes. Am J Med 123: S2.
23. Drewes AM (1999) Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. Rheumatology (Oxford) 38: 1035-1038.
24. Sergi M, Rizzi M, Braghiroli A, Puttini PS, Greco M, et al. (1999) Periodic breathing during sleep in patients affected by fibromyalgia syndrome. Eur Respir J 14: 203-208.
25. Harding SM (1998) Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 315: 367-376.
26. Bengtsson A, Henriksson KG, Jorfeldt L, Kågedal B, Lennmarken C, et al. (1986) Primary fibromyalgia. A clinical and laboratory study of 55 patients. Scand J Rheumatol 15: 340-347.
27. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L (2007) An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 8: 27.
28. Häuser W, Zimmer C, Felde E, Köllner V (2008) What are the key symptoms of fibromyalgia? Results of a survey of the German Fibromyalgia Association. Schmerz 22: 176-183.
29. Mease P, Arnold LM, Choy E H, Cauw DJ, Crofford LJ, Glass JM, et al. (2009) Fibromyalgia syndrome module at OMERACT 9: domain construct. Journal of Rheumatology 36: 2318-2329..
30. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S (2001) Alpha sleep characteristics in fibromyalgia. Arthritis Rheum 44: 222-230.
31. Anch AM, Lue FA, MacLean AW, Moldofsky H (1991) Sleep physiology and psychological aspects of the fibrositis (fibromyalgia) syndrome. Can J Psychol 45: 179-184.
32. Branco J, Atalaia A, Paiva T (1994) Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. J Rheumatol 21: 1113-1117.
33. Drewes AM, Gade K, Nielsen KD, Bejerregard K, Taagholt SJ, et al. (1995) Clustering of sleep electroencephalographic patterns in patients with the fibromyalgia syndrome. British Journal of Rheumatology 34: 1151-1156.
34. Pivik RT, Harman K (1995) A reconceptualization of EEG alpha activity as an index of arousal during sleep: all alpha activity is not equal. J Sleep Res 4: 131-137.
35. Horne JA, Shackell BS (1991) Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. Electroencephalogr Clin Neurophysiol 79: 271-276.
36. Drewes AM, Nielsen KD, Taagholt SJ, Bjerregård K, Svendsen L, et al. (1995) Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. Br J Rheumatol 34: 629-635.
37. Chervin RD, Teodorescu M, Kushwaha R, Deline AM, Brucksch CB, et al. (2009) Objective measures of disordered sleep in fibromyalgia. J Rheumatol 36: 2009-2016.
38. Landis CA, Lentz MJ, Rothermel J, Buchwald D, Shaver JL (2004) Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain. Sleep 27: 741-750.
39. Burns JW, Crofford LJ, Chervin RD (2008) Sleep stage dynamics in fibromyalgia patients and controls. Sleep Med 9: 689-696.
40. Rizzi M, Sarzi-Puttini P, Atzeni F, Capsoni F, Andreoli A, et al. (2004) Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? J Rheumatol 31: 1193-1199.
41. Klerman EB, Goldenberg DL, Brown EN, Maliszewski AM, Adler GK (2001) Circadian rhythms of women with fibromyalgia. J Clin Endocrinol Metab 86: 1034-1039.
42. Adler GK, Kinsley BT, Hurwitz S, Mossey CJ, Goldemberg DL (1999) Reduced hypothalamic-pituitary and syumpathoadrenal responses to hypoglicemia in women with fibromyalgia in women with fibromyalgia syndrome. Am J Med 840: 684-697.
43. Demitrack MA, Crofford LJ (2002) Evidence for and pathophysiologic implications of hypothalamic-pituitary-adreanl axis dysregulation in fibromyalgia and chronic fatigue syndrome. Current Rheumattol. Reports 4: 306-312.
44. Bennett RM (2002) Adult growth hormone deficiency in patients with fibromyalgia. Curr Rheumatol Rep 4: 306-312.
45. Paiva ES, Deodhar A, Jones KD, Bennett R (2002) Impairment growth hormone secretion in fibromyalgia patients: evidence for augmented hypothalamic somatostatin tone. Artritis and Rheumatism 46: 1344-1350.
46. Leal-Cerro A, Povedano J, Astorga R, Gonzalez M, Silva H, et al. (1999) The growth hormone (GH)-releasing hormone-GH-insulin-like growth factor-1 axis in patients with fibromyalgia syndrome. J Clin Endocrinol Metab 84: 3378-3381.
47. Moutz JM, Bradley LA, Modell JG, Alexander RW, Alexander M, et al. (1995) Fibromyalgia in women: abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Artritis Rheum 38: 926-938.
48. Culebras A, Miller M (1984) Dissociated patterns of nocturnal prolactin, cortisol and growth hormone secretion after stroke. Neurology 34: 631-636.
49. Van Cauter E, Plat L, Copinschi G (1998) Interrelations between sleep and the somatotropic axis. Sleep 21: 553-566.
50. Prinz PN, Moe KE, Dulberg EM, Larsen LH, Vitiello MV, et al. (1995) Higher plasma IGF-1 levels are associated with increased delta sleep in healthy older men. Journal of Gerontology Series A Biological Sciences and medical Sciences 50: 222-226.
51. Bennett RM, Clark SR, Campbell SM, Burckhardt CS (1992) Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. Arthritis Rheum 35: 1113-1116.
52. Bennett RM, Clark SC, Walczyk J (1998) A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. Am J Med 104: 227-231.
53. Vaerøy H, Helle R, Førre O, Kåss E, Terenius L (1988) Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. Pain 32: 21-26.
54. Cooper JR, Bloom FE, Roth RH (1986) The biochemical basis of neuropharmacology. New York: Oxford University Press: 362-366.
55. Andersen ML, Nascimento DC, Machado RB, Roizenblatt S, Moldofsky H, et al. (2006) Sleep disturbance induced by substance P in mice. Behav Brain Res 167: 212-218.
56. Almeida TF, Roizenblatt S, Benedito-Silva AA, Tufik S (2003) The effect of combined therapy (ultrasound and interferential current) on pain and sleep in fibromyalgia. Pain 104: 665-672.
57. Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, et al. (2007) Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract 7: 297-306.
58. Crofford LJ, Rowbotham MC, Mease PJ, Russel IJ, Dworkin RH, et al (2005) Pregabalin study group 1008-105. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized , double-blind, placebo-controlled trial. Arthritis and Rheumatism 52: 1264-1273.
59. Häuser W, Petzke F, Sommer C (2010) Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 11: 505-521.
60. Häuser W, Petzke F, Üçeyler N, Sommer C (2011) Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford) 50:

532-543.

61. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, et al. (2009) The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. J Rheumatol 36: 398-409.
62. Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, et al. (2009) The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med 10: 604-610.
63. Chalon S, Pereira A, Lainey E, Vandenhende F, Watkin JG, et al. (2005) Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. Psychopharmacology (Berl) 177: 357-365.
64. Arnold LM, Clauw D, Wang F, Ahl J, Gaynor PJ, et al. (2010) Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. J Rheumatol 37: 2578-2586.
65. Curry DT, Eisenstein RD, Walsh JK (2006) Pharmacologic management of insomnia: past, present, and future. Psychiatr Clin North Am 29: 871-893.
66. Ferguson SA, Rajaratnam SM, Dawson D (2010) Melatonin agonists and insomnia. Expert Rev Neurother 10: 305-318.
67. Scharf MB, Baumann M, Berkowitz DV (2003) The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol 30: 1070-1074.
68. Wolfe F, Clauw DJ, Fitzcharles MA, Goldemberg DL, Kartz RS, et al (2010) The American college of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Research (Hoboken) 62: 600-610.
69. Harding SM (1998) Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 315: 367-376.
70. Sateia MJ, Doghramji K, Hauri PJ, Morin CM (2000) Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep 23: 243-308.
71. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, et al (2005) Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 28: 499-521.