BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH
www.bjournal.com.br

ISSN 0100-879X
Volume 45 (9) 792-874 September 2012

CLINICAL INVESTIGATION

Braz J Med Biol Res, September 2012, Volume 45(9) 792-798

doi: 10.1590/S0100-879X2012007500110

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Brazilian Journal of Medical and Biological Research (2012) 45: 792-798
ISSN 0100-879X Review

# Pain-related diseases and sleep disorders

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## Abstract

Pain and sleep share mutual relations under the influence of cognitive and neuroendocrine changes. Sleep is an important homeostatic feature and, when impaired, contributes to the development or worsening of pain-related diseases. The aim of the present review is to provide a panoramic view for the generalist physician on sleep disorders that occur in pain-related diseases within the field of Internal Medicine, such as rheumatic diseases, acute coronary syndrome, digestive diseases, cancer, and headache.

Key words: Sleep disorders; Rheumatic diseases; Acute coronary syndrome; Irritable bowel syndrome; Cancer; Headache

## Introduction

Pain and sleep influence one another. Pain may be exacerbated by sleep disorders (1) while sleep is impaired by pain (2). The concept of pain-on and pain-off neurons may explain the anatomical interactions of pain and sleep phenomena. These neurons, which are situated in the nucleus raphe magnus, respectively facilitate and inhibit nociceptive impulses to thalamocortical pathways and are influenced by the wake-sleep cycle: inhibitory pain-off nerve cells are completely activated during deep sleep while excitatory pain-on nerve cells are activated during wakefulness (3). In this context, serotonin plays a role in promoting both analgesia and deep sleep (4).

Neuroendocrine and autonomic mechanisms may influence and be influenced by pain and sleep. Concerning chronic widespread pain syndromes, sleep disorders and nociceptive afference are important to elevate the sympathetic tonus, which my lead to vascular remodeling, muscular atrophy and fatigue (5).

Pain and sleep disturbances may generate or perpetuate cognitive, affective and motivational dysfunctions, which, in turn, promote hypervigilance and frequent awakenings. This is explained by the sharing of common afferent circuits such as the parabrachial-amygdala and parabrachial-hypothalamic pathways (6).

Less than 6 h of sleep may contribute to pain manifestations the following day (7). Similarly, sleep deprivation, especially of deep sleep, results in wakening unrefreshed with widespread pain and fatigue in healthy sedentary individuals. In this context, alpha wave (8-10 Hz) activity inappropriately intrudes during delta wave (0.5-3.5 Hz) activity (8-10).

The restoration of adequate sleep is essential to avoid exacerbation of painful symptoms (11). In the case of REM sleep deprivation, a reduced pain threshold persists for a variable period of time, even after normal sleep has been restored (12).

## Rheumatic diseases

Sleep disorders have been described in more than 75% of subjects suffering from various forms of rheumatic diseases and fatigue is observed in up to 98% of cases (13). Modifications of pain mediators, such as serotonin and substance P, and of neuroimmune mechanisms, such as inflammatory cytokines (interleukin-1 and tumor necrosis factor-α, TNF-α) and cell-mediated immunity have been also described. Moreover, there is the involvement of neuroendocrine mechanisms, such as the hypothalamic-pituitary-adrenal axis and the thyroid, alongside the autonomic nervous system (13).

In general, there is reduced sleep efficiency accompanied by increased periods of wakefulness during the night. Sleep is typically superficial and disrupted and primary sleep disorders are frequent in these conditions, such as periodic limb movements and sleep apnea (14).

Pain, sleep disturbance and depression are predictors

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*Received March 13, 2012. Accepted June 25, 2012. Available online July 6, 2012. Published August 17, 2012.*

of the severe fatigue that occurs in rheumatoid arthritis, osteoarthritis, and fibromyalgia (15). The relationship between pain and sleep disorders in rheumatic diseases has been observed not only in fibromyalgia (16) and rheumatoid arthritis (15), but also in low back pain (17), osteoarthritis (18), ankylosing spondylitis (19), Sjögren's syndrome (20), systemic lupus erythematosus (21), systemic sclerosis (22), and soft-tissue disorders (23).

## Fibromyalgia

The importance of non-restorative sleep, which affects more than 90% of patients, is such that this manifestation is now included among the new diagnostic criteria (24). The non-restorative sleep and increased wake time after sleep onset act as predictors of pain and fatigue and have social implications, even when anxiety and depression are excluded (25).

An electroencephalographic pattern of alpha wave intrusion in delta wave sleep (alpha-delta sleep) has been described in fibromyalgia (16), but also in other chronic widespread pain conditions, and even in healthy individuals. The phasic alpha-delta pattern, in which the distribution of alpha activity overlaps the delta activity, especially during slow-wave sleep (26), suggests that there is a disturbance in fibromyalgia sleep homeostasis mediated by pain stimuli that lead to awakening (27); however, studies have included a small sample size of patients. Other authors focused on the cyclic alternating pattern of non-REM sleep to explain the relationship of altered sleep and pain perception (28) and some controversial studies have reported reduction in total sleep time and in sleep efficiency and modification of sleep stage distribution, with a predominance of light sleep compared to deep sleep, instead of sleep instability (29).

Changes in heart rate variability have also been described in patients with fibromyalgia, reflecting sympathetic hyperactivity in contrast to hyporesponsiveness against sympathetic stimulation, or during sleep (30).

A higher prevalence of upper airway resistance syndrome in patients with fibromyalgia (31) may not reflect a direct relationship between the two conditions, since musculoskeletal pain may be attributed to restricted physical activity in obstructive sleep apnea (32).

The approval of Pregabaline, a derivative of γ-aminobutyric acid (GABA) that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities, has been a real advance for the management of non-restorative sleep in fibromyalgia (33), and odium oxybate, a metabolite of dopamine, which increases GABA, has recently been proposed to increase slow-wave sleep and decrease sleep disruption (34).

## Osteoarthritis

Clinical symptoms of osteoarthritis tend to be exacerbated at night and on awakening. The involvement of the lumbar spine (17), knee or hip (18) can impair sleep onset and maintenance. The findings of sleep fragmentation due to increased number of arousals (35) and periodic limb movements (36) may explain fatigue and joint stiffness (of less than 30 min) upon awakening, which are frequently reported by the patients.

## Soft tissue disorders

Sleep studies are only available for carpal tunnel syndrome. Patients may complain of nocturnal and early morning awakenings with hand pain and numbness. Non-restorative sleep, daytime sleepiness and polysonographic findings such as arousals and periodic limb movement indexes tend to improve after surgical treatment of the affected wrist (23). However, carpal tunnel syndrome may be the presenting symptom of underlying diabetes mellitus, hypothyroidism or connective tissue disease, which are also associated with sleep disorders.

Many investigators have tried to explain why tendonitis, tenosynovitis, bursitis, and periarthritis tend to worsen at night, as described for shoulder-related disorders, but the reasons are still unclear and deserve more study (37).

## Ankylosing spondylitis

Up to 80% of patients with ankylosing spondylitis tend to wake during the night in need of walking in order to get some relief of low back pain. Polysomnography shows increased sleep latency and fragmented sleep (19), which can be the result of functional, often motor, disabilities. Fatigue is a prominent symptom of ankylosing spondylitis, reported by more than half the patients, and is associated with functional disability (38). Also, patients complain about excessive daytime sleepiness and the frequent need for naps (39). Arthritis, costochondral inflammation and enthesitis gradually lead to spine ankylosis and chest wall rigidity and obstructive sleep apnea, when present, further aggravates the respiratory condition of the patients (40). Anti-TNF agents improve both sleep disorders and inflammatory activity and shed light on the pathophysiology of the disease (41).

## Rheumatoid arthritis

Morning stiffness differs from osteoarthritis because in rheumatoid arthritis it lasts more than 1 h and in osteoarthritis, less than 30 min (42). Additionally, association between clinical manifestations of the disease and fatigue, excessive daytime sleepiness and sleep alterations has been reported (43). Decreased sleep efficiency, superficial sleep, reduction in REM sleep, and an increase in the number of arousals (44) may exacerbate sleep fragmentation and fatigue, as well as periodic limb movements (45) and sleep apnea (46). Skeletal abnormalities, particularly of

the temporomandibular joint and the cervical spine may underlie sleep apnea in rheumatoid arthritis (47). As reported in ankylosing spondylitis, improvement of the sleep apnea and the fatigue following administration of TNF-α blockers has been demonstrated (48).

## Sjögren's syndrome

Prominent fatigue is very commonly reported by patients and is related to sleep disorders, musculoskeletal pain, anxiety (49), and fibromyalgia, which occurs in 55% of the patients (50). Polysomnographic findings reflect the non-restorative sleep condition reported by the patients, with reduction in sleep efficiency, intermediate awakenings (20) and rhythmic oral movements attributed to the lack of saliva (51).

## Systemic lupus erythematosus

Besides prominent fatigue that is the hallmark of rheumatic diseases with a remarkable autoimmune component (21), and polysomnography findings of increased sleep latency and reduced total sleep time, not related to depression (52), co-morbidities play an important role in pain and sleep interactions in systemic lupus erythematosus. Obesity, neuropsychiatric and kidney involvement and the use of medications such as antihistamines and glucocorticoids may act as confounders when restless legs syndrome (53) and sleep apnea (54) are present.

## Scleroderma

Fatigue and poor sleep are also frequent complaints in scleroderma (55). In addition, sleep disturbances may aggravate the manifestations of the disease. The presence of sleep apnea may contribute to endothelial damage, particularly in the lungs, periodic limb movements may aggravate nocturnal pain due to ischemia and the presence of gastroesophageal reflux may contribute to the fragmentation of sleep and fatigue (22).

## Coronary heart disease

Among the changes in sleep architecture in acute coronary syndromes, the most frequent are difficulty of initiating and maintaining sleep, the presence of arousals and reduced total sleep time. It has been hypothesized that both quantity and quality of sleep have a negative influence on patient recovery (56). Superficial and disrupted sleep is described in 60% of patients with coronary artery disease and is compared to the hypervigilance observed in post-traumatic stress disorder (57).

Sleep disorders in patients with coronary artery diseases may aggravate myocardial ischemia. Given that cytokines modulate sleep, an immune substrate has been considered to explain insomnia and parasomnias, such as nightmares, which may precede an acute coronary syndrome. Moreover, hypoxemia due to obstructive sleep apnea, when present, promotes the deterioration of cardiac ischemia (58).

## Digestive tract diseases

### Irritable bowel syndrome

Complaints of abdominal cramps and flatulence persist during the night, awakening the patient. Sleep fragmentation leads to poor sleep, which, in turn, promotes deterioration of intestinal symptoms (59). In addition, patients have altered perception of their sleep, considering that it has not been established that sleep latency or efficiency are altered in irritable bowel syndrome (60). Autonomic dysfunction, in terms of increased sympathetic tonus during REM sleep, may underlie the relationship between disease activity and sleep fragmentation (61).

### Gastroesophageal reflux disease

Although the frequency of gastroesophageal reflux is highest during wakefulness, its presence during sleep has a greater impact on the quality of life of the patients. This is because night reflux lasts longer and saliva production is reduced. In addition to the sleep fragmentation and early awakening, gastroesophageal reflux causes respiratory symptoms such as coughing and wheezing. Aspiration of gastric acid reflux into the larynx is common in individuals with asthma (62). The stimulation of vagal nerve afferents in the distal esophagus by the presence of gastric acid reflux supports the treatment of the disease when present in asthma patients. Lifestyle modifications and eating light meals at night at least 2 h before bedtime, are advised even when there is indication for surgery. Additionally, raising the head of the bed and sleeping in left lateral position are recommended in order to reduce esophageal acid exposure and to increase esophageal clearance of gastric contents. The association of proton pump inhibitors helps improve sleep quality (63).

## Neoplastic diseases

The combination of pain, fatigue and sleep disturbances is reported by more than 40% of cancer patients (64). Pain occurs in 59% of individuals under treatment for cancer and 64% of those with advanced disease (65). Fatigue affects most patients, especially after surgical procedures, chemotherapy, immunotherapy and radiotherapy. Fatigue, excessive sleepiness and restless legs syndrome may all be associated with anemia and iron deficiency and occur particularly in lung, breast, genitourinary, gastrointestinal, and non-melanoma skin cancer (66).

Besides fragmented and superficial sleep, reported in up to 72% of the cases (67), screening for the presence of sleep apnea is appropriate in patients with oral or oropharynx

cancer before and after treatment (68).

Treatment of insomnia may improve fatigue and even immunity in cancer patients. However, sedatives and sleep inducers may result in lack of attention or drowsiness during the day, which could enhance fatigue and muscle pain and reduce the pain threshold (69). Moreover, pain killers and steroids may aggravate the symptoms of fatigue, increase daytime sleep and worsen non-restorative sleep (70), and opioids may contribute to the emergence of central apnea during sleep (71). In addition, side effects of chemotherapy, pain, nausea, diarrhea, and urinary urgency facilitate sleep fragmentation (68). Such interruptions invariably result in insufficient rest and increased fatigue. It is worth noting the value of behavioral psychological intervention that improves sleep quality and cancer-related fatigue (72).

## Headaches

There is a strong interface between sleep disorders and headaches. Even though a causal link between the two conditions has not yet been established, improvement in sleep quality results in improvement of headache, especially in cases of sleep deprivation (73).

The relationship between sleep-wake cycle and the various types of headaches, such as migraine, cluster headache and paroxysmal hemicrania, is due to the activation of the posterior hypothalamus. Brain stem and diencephalon pathways in headaches are related to sleep fragmentation, as also described for visceral pain (74).

Sleep disorders are found in patients with morning or night occurring migraine. The circadian periodicity in morning migraine is related to REM sleep and glucocorticoids and catecholamine cycles (73). Night migraine, in turn, may involve alterations in the regulatory mechanisms of awakenings during sleep. Crises tend to be preceded by episodes of yawning. Despite the fragmented sleep during periods of crises, fewer awakenings have been described in the night preceding the night migraine episodes (75).

Cluster headaches tend to predominate in the early morning hours and 90 min after sleep onset. The substrate of their association with REM sleep is secretion of melatonin and cortisol (76). Paroxysmal hemicrania also has a certain relation to REM sleep (77). In contrast, hypnic headache tends to awaken the patient in the first half of the night for at least 15 nights a month. Interestingly, treatment of sleep fragmentation tends to improve chronic migraine, tension headache, cluster headache, and hypnic headache pain intensity (78). Insomnia and nonrestorative sleep have been recognized as risk factors for chronification of tension headache, migraine and medication overuse headache (79) and restoration of sleep quality, in turn, reverses the condition (80).

A possible link between primary headaches and narcolepsy has been proposed to be due to a higher frequency of migraine in patients with narcolepsy, especially in women, which may experience episodes of narcolepsy prior to the migrainous attacks (81). The polymorphism of receptor-2 of the gene encoding orexin/hypocretin, which is involved in the sleep-wake cycle in narcolepsy and in pain modulation, has been described in individuals with cluster headaches (82). It is, therefore, evident that the damage of lateral hypothalamic orexinergic neurons affects the activation of REM-off neurons that disrupt REM sleep. These neurons in the ventrolateral periaqueductal gray substance are also involved in the reduction of nociceptive activity in the trigeminal and caudate nucleus and their inhibition favors pain mechanisms (81).

The correlation between severity of migraine and the presence of restless legs syndrome may demonstrate that migraine may also have a substrate of dopaminergic impairment (83), iron metabolism imbalance (84) and depression (85), as occurs in restless legs syndrome.

In morning and night migraine, 30-70% of patients have obstructive sleep apnea or intense snoring (86). Cluster headache and paroxysmal hemicranic headache, particularly in its chronic form, are also more frequent in subjects with obstructive sleep apnea than in the general population (87). Conversely, 15-74% of patients with obstructive sleep apnea wake up with headache, and in 48% of cases the headache pattern cannot be classified (88). Nocturnal awakenings accompanied by intense headache crises in individuals with obstructive sleep apnea have been associated with intracranial hypertension (89).

Possible pathophysiological bases for the association between headache and sleep apnea are hypoxemia and hypercapnia, since symptoms improved after treatment with continuous positive airway pressure (CPAP) or supplemental oxygen (88). Morning migraine related to sleep apnea is more prevalent in women with moderate to severe apnea and in subjects with a history of primary headache, and tends to improve with the use of CPAP (90). Likewise, the benefit of CPAP is observed in cluster headaches triggered by oxyhemoglobin desaturation, especially during REM sleep (87).

## Conclusion

The generalist physician should be aware of the contribution of sleep to the initiation or worsening of diseases that have pain as a prominent manifestation. Further reviews are warranted to discuss the pathophysiology underlying such association.

## References


1. Chiu YH, Silman AJ, Macfarlane GJ, Ray D, Gupta A, Dickens C, et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain* 2005; 115: 316-321.
2. Ohayon MM. Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res* 2005; 39: 151-159.
3. Foo H, Mason P. Brainstem modulation of pain during sleep and waking. *Sleep Med Rev* 2003; 7: 145-154.
4. Leung CG, Mason P. Physiological properties of raphe magnus neurons during sleep and waking. *J Neurophysiol* 1999; 81: 584-595.
5. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006; 47: 833-839.
6. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci* 2008; 12: 306-313.
7. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev* 2006; 10: 357-369.
8. Older SA, Battafarano DF, Danning CL, Ward JA, Grady EP, Derman S, et al. The effects of delta wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects; correlations with insulin-like growth factor I. *J Rheumatol* 1998; 25: 1180-1186.
9. 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.
10. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001; 10: 35-42.
11. Tang NK. Cognitive-behavioral therapy for sleep abnormalities of chronic pain patients. *Curr Rheumatol Rep* 2009; 11: 451-460.
12. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006; 29: 145-151.
13. Moldofsky H. Rheumatic manifestations of sleep disorders. *Curr Opin Rheumatol* 2010; 22: 59-63.
14. Moldofsky H. Sleep and pain. *Sleep Med Rev* 2001; 5: 385-396.
15. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-1417.
16. Moldofsky H, Scarisbrick P, England R, Smythe H. Musculosketal symptoms and non-REM sleep disturbance in patients with “fibrositis syndrome” and healthy subjects. *Psychosom Med* 1975; 37: 341-351.
17. Kelly GA, Blake C, Power CK, O’Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. *Clin J Pain* 2011; 27: 169-181.
18. Allen KD, Renner JB, DeVellis B, Helmick CG, Jordan JM. Osteoarthritis and sleep: the Johnston County Osteoarthritis Project. *J Rheumatol* 2008; 35: 1102-1107.
19. Heiberg T, Lie E, van der Heijde D, Kvien TK. Sleep problems are of higher priority for improvement for patients with ankylosing spondylitis than for patients with other inflammatory arthropathies. *Ann Rheum Dis* 2011; 70: 872-873.
20. Gudbjornsson B, Broman JE, Hetta J, Hallgren R. Sleep disturbances in patients with primary Sjogren’s syndrome. *Br J Rheumatol* 1993; 32: 1072-1076.
21. Valencia-Flores M, Resendiz M, Castano VA, Santiago V, Campos RM, Sandino S, et al. Objective and subjective sleep disturbances in patients with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 2189-2193.
22. Milette K, Razykov I, Pope J, Hudson M, Motivala SJ, Baron M, et al. Clinical correlates of sleep problems in systemic sclerosis: the prominent role of pain. *Rheumatology* 2011; 50: 921-925.
23. Lehtinen I, Kirjavainen T, Hurme M, Lauerma H, Martikainen K, Rauhala E. Sleep-related disorders in carpal tunnel syndrome. *Acta Neurol Scand* 1996; 93: 360-365.
24. Wolfe F, Hauser W. Fibromyalgia diagnosis and diagnostic criteria. *Ann Med* 2011; 43: 495-502.
25. Staud R. Predictors of clinical pain intensity in patients with fibromyalgia syndrome. *Curr Pain Headache Rep* 2005; 9: 316-321.
26. Roizenblatt S, Moldofsky H, Bemedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum* 2001; 44: 222-230.
27. Drewes AM, Nielsen KD, Arendt-Nielsen L, Birket-Smith L, Hansen LM. The effect of cutaneous and deep pain on the electroencephalogram during sleep - an experimental study. *Sleep* 1997; 20: 632-640.
28. Rizzi M, Sarzi-Puttini P, Atzeni F, Capsoni F, Andreoli A, Pecis M, et al. Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? *J Rheumatol* 2004; 31: 1193-1199.
29. Roizenblatt S, Neto NS, Tufik S. Sleep disorders and fibromyalgia. *Curr Pain Headache Rep* 2011; 15: 347-357.
30. Chervin RD, Teodorescu M, Kushwaha R, Deline AM, Brucksch CB, Ribbens-Grimm C, et al. Objective measures of disordered sleep in fibromyalgia. *J Rheumatol* 2009; 36: 2009-2016.
31. Gold AR, Dipalo F, Gold MS, Broderick J. Inspiratory airflow dynamics during sleep in women with fibromyalgia. *Sleep* 2004; 27: 459-466.
32. Potter PJ. Musculoskeletal complaints and fibromyalgia in patients attending a respiratory sleep disorders clinic. *J Rheumatol* 1997; 24: 1657-1658.
33. Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. *Arthritis Care Res* 2012; 64: 597-606.
34. 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.
35. O’Donoghue GM, Fox N, Heneghan C, Hurley DA. Objective and subjective assessment of sleep in chronic low back pain patients compared with healthy age and gender matched controls: a pilot study. *BMC Musculoskelet Disord* 2009; 10: 122.

36. Power JD, Badley EM, French MR, Wall AJ, Hawker GA. Fatigue in osteoarthritis: a qualitative study. *BMC Musculoskelet Disord* 2008; 9: 63.
37. Zenian J. Sleep position and shoulder pain. *Med Hypotheses* 2010; 74: 639-643.
38. Missaoui B, Revel M. Fatigue in ankylosing spondylitis. *Ann Readapt Med Phys* 2006; 49: 305-391.
39. Aissaoui N, Rostom S, Hakkou J, Berrada GK, Bahiri R, Abouqal R, et al. Fatigue in patients with ankylosing spondylitis: prevalence and relationships with disease-specific variables, psychological status, and sleep disturbance. *Rheumatol Int* 2011 [Epub ahead of print].
40. Solak O, Fidan F, Dundar U, Turel A, Aycicek A, Kavuncu V, et al. The prevalence of obstructive sleep apnoea syndrome in ankylosing spondylitis patients. *Rheumatology* 2009; 48: 433-435.
41. Karadag O, Nakas D, Kalyoncu U, Akdogan A, Kiraz S, Ertenli I. Effect of anti-TNF treatment on sleep problems in ankylosing spondylitis. *Rheumatol Int* 2011 [Epub ahead of print].
42. Sokka T. Morning stiffness and other patient-reported outcomes of rheumatoid arthritis in clinical practice. *Scand J Rheumatol Suppl* 2011; 125: 23-27.
43. Luyster FS, Chasens ER, Wasko MC, Dunbar-Jacob J. Sleep quality and functional disability in patients with rheumatoid arthritis. *J Clin Sleep Med* 2011; 7: 49-55.
44. Bourguignon C, Labyak SE, Taibi D. Investigating sleep disturbances in adults with rheumatoid arthritis. *Holist Nurs Pract* 2003; 17: 241-249.
45. Taylor-Gjevre RM, Gjevre JA, Skomro R, Nair B. Restless legs syndrome in a rheumatoid arthritis patient cohort. *J Clin Rheumatol* 2009; 15: 12-15.
46. Reading SR, Crowson CS, Rodeheffer RJ, Fitz-Gibbon PD, Maradit-Kremers H, Gabriel SE. Do rheumatoid arthritis patients have a higher risk for sleep apnea? *J Rheumatol* 2009; 36: 1869-1872.
47. Shoda N, Seichi A, Takeshita K, Chikuda H, Ono T, Oka H, et al. Sleep apnea in rheumatoid arthritis patients with occipitocervical lesions: the prevalence and associated radiographic features. *Eur Spine J* 2009; 18: 905-910.
48. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. *J Clin Endocrinol Metab* 2004; 89: 4409-4413.
49. Theander L, Strombeck B, Mandl T, Theander E. Sleepiness or fatigue? Can we detect treatable causes of tiredness in primary Sjogren's syndrome? *Rheumatology* 2010; 49: 1177-1183.
50. Tishler M, Barak Y, Paran D, Yaron M. Sleep disturbances, fibromyalgia and primary Sjogren's syndrome. *Clin Exp Rheumatol* 1997; 15: 71-74.
51. Thie NM, Kato T, Bader G, Montplaisir JY, Lavigne GJ. The significance of saliva during sleep and the relevance of oromotor movements. *Sleep Med Rev* 2002; 6: 213-227.
52. McKinley PS, Ouellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. A proposed model. *Arthritis Rheum* 1995; 38: 826-834.
53. Hassan N, Pineau CA, Clarke AE, Vinet E, Ng R, Bernatsky S. Systemic lupus and risk of restless legs syndrome. *J Rheumatol* 2011; 38: 874-876.
54. Iaboni A, Ibanez D, Gladman DD, Urowitz MB, Moldofsky H. Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression. *J Rheumatol* 2006; 33: 2453-2457.
55. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997; 40: 1984-1991.
56. Schiza SE, Simantirakis E, Bouloukaki I, Mermigkis C, Arfanakis D, Chrysostomakis S, et al. Sleep patterns in patients with acute coronary syndromes. *Sleep Med* 2010; 11: 149-153.
57. Doerfler LA, Paraskos JA. Post-traumatic stress disorder in patients with coronary artery disease: screening and management implications. *Can J Cardiol* 2005; 21: 689-697.
58. Asplund R. Nightmares, sleep and cardiac symptoms in the elderly. *Neth J Med* 2003; 61: 257-261.
59. Mathieu N. [Somatic comorbidities in irritable bowel syndrome: fibromyalgia, chronic fatigue syndrome, and interstitial cystitis]. *Gastroenterol Clin Biol* 2009; 33 (Suppl 1): S17-S25.
60. Heitkemper M, Jarrett M, Burr R, Cain KC, Landis C, Lentz M, et al. Subjective and objective sleep indices in women with irritable bowel syndrome. *Neurogastroenterol Motil* 2005; 17: 523-530.
61. Thompson JJ, Elsenbruch S, Harnish MJ, Orr WC. Autonomic functioning during REM sleep differentiates IBS symptom subgroups. *Am J Gastroenterol* 2002; 97: 3147-3153.
62. Cuttitta G, Cibella F, Visconti A, Scichilone N, Bellia V, Bonsignore G. Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics. *Am J Respir Crit Care Med* 2000; 161: 177-181.
63. Johnson DA, Orr WC, Crawley JA, Traxler B, McCullough J, Brown KA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *Am J Gastroenterol* 2005; 100: 1914-1922.
64. Kwekkeboom KL, Cherwin CH, Lee JW, Wanta B. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. *J Pain Symptom Manage* 2010; 39: 126-138.
65. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007; 18: 1437-1449.
66. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. *Soc Sci Med* 2002; 54: 1309-1321.
67. Vena C, Parker K, Cunningham M, Clark J, McMillan S. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. *Oncol Nurs Forum* 2004; 31: 735-746.
68. Parish JM. Sleep-related problems in common medical conditions. *Chest* 2009; 135: 563-572.
69. Zee PC, Ancoli-Israel S. Does effective management of sleep disorders reduce cancer-related fatigue? *Drugs* 2009; 69 (Suppl 2): 29-41.
70. Gianni W, Ceci M, Bustacchini S, Corsonello A, Abbatecola AM, Brancati AM, et al. Opioids for the treatment of chronic non-cancer pain in older people. *Drugs Aging* 2009; 26 (Suppl 1): 63-73.
71. Hardy JR, Bowler SD. Central sleep apnea in cancer pa-

tients on opioids. *J Pain Symptom Manage* 2010; 40: e3-e5.
72. Berger AM. Update on the state of the science: sleep-wake disturbances in adult patients with cancer. *Oncol Nurs Forum* 2009; 36: E165-E177.
73. Paiva T. Sleep and headache. *Handb Clin Neurol* 2011; 99: 1073-1086.
74. Brennan KC, Charles A. Sleep and headache. *Semin Neurol* 2009; 29: 406-418.
75. Goder R, Fritzer G, Kapsokalyvas A, Kropp P, Niederberger U, Strenge H, et al. Polysomnographic findings in nights preceding a migraine attack. *Cephalalgia* 2001; 21: 31-37.
76. Leone M, Lucini V, D'Amico D, Moschiano F, Maltempo C, Fraschini F, et al. Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. *Cephalalgia* 1995; 15: 224-229.
77. Liang JF, Fuh JL, Yu HY, Hsu CY, Wang SJ. Clinical features, polysomnography and outcome in patients with hypnic headache. *Cephalalgia* 2008; 28: 209-215.
78. Rains JC. Chronic headache and potentially modifiable risk factors: screening and behavioral management of sleep disorders. *Headache* 2008; 48: 32-39.
79. Fuh JL, Wang SJ, Lu SR, Juang KD. Does medication overuse headache represent a behavior of dependence? *Pain* 2005; 119: 49-55.
80. Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. *Headache* 2007; 47: 1178-1183.
81. Dahmen N, Kasten M, Wieczorek S, Gencik M, Epplen JT, Ullrich B. Increased frequency of migraine in narcoleptic patients: a confirmatory study. *Cephalalgia* 2003; 23: 14-19.
82. Rainero I, Rubino E, Valfre W, Gallone S, De Martino P, Zampella E, et al. Association between the G1246A polymorphism of the hypocretin receptor 2 gene and cluster headache: a meta-analysis. *J Headache Pain* 2007; 8: 152-156.
83. D'Onofrio F, Bussone G, Cologno D, Petretta V, Buzzi MG, Tedeschi G, et al. Restless legs syndrome and primary headaches: a clinical study. *Neurol Sci* 2008; 29 (Suppl 1): S169-S172.
84. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia* 2010; 30: 129-136.
85. Rhode AM, Hosing VG, Happe S, Biehl K, Young P, Evers S. Comorbidity of migraine and restless legs syndrome - a case-control study. *Cephalalgia* 2007; 27: 1255-1260.
86. Ulfberg J, Carter N, Talback M, Edling C. Headache, snoring and sleep apnoea. *J Neurol* 1996; 243: 621-625.
87. Mitsikostas DD, Vikelis M, Viskos A. Refractory chronic headache associated with obstructive sleep apnoea syndrome. *Cephalalgia* 2008; 28: 139-143.
88. Rains JC, Poceta JS. Sleep and headache. *Curr Treat Options Neurol* 2010; 12: 1-15.
89. Bruce BB, Kedar S, Van Stavern GP, Monaghan D, Acierno MD, Braswell RA, et al. Idiopathic intracranial hypertension in men. *Neurology* 2009; 72: 304-309.
90. Goksan B, Gunduz A, Karadeniz D, Agan K, Tascilar FN, Tan F, et al. Morning headache in sleep apnoea: clinical and polysomnographic evaluation and response to nasal continuous positive airway pressure. *Cephalalgia* 2009; 29: 635-641.