The role of sleep in pain and fibromyalgia

Ernest H. S. Choy

Abstract | Fibromyalgia is a common cause of chronic widespread pain, characterized by reduced pressure pain thresholds with hyperalgesia and allodynia. In addition to pain, common symptoms include nonrestorative sleep, fatigue, cognitive dysfunction, stiffness and mood disturbances. The latest research indicates that the dominant pathophysiology in fibromyalgia is abnormal pain processing and central sensitization. Neuroimaging studies have shown that patients with fibromyalgia have similar neural activation to healthy age-matched and gender-matched individuals; however, they have a lower pressure-pain threshold. Polysomnography data has demonstrated that these patients have reduced short-wave sleep and abnormal α-rhythms, suggestive of wakefulness during non-REM (rapid eye movement) sleep. Sleep deprivation in healthy individuals can cause symptoms of fibromyalgia, including myalgia, tenderness and fatigue, suggesting that sleep dysfunction might be not only a consequence of pain, but also pathogenic. Epidemiological studies indicate that poor sleep quality is a risk factor for the development of chronic widespread pain among an otherwise healthy population. Mechanistically, sleep deprivation impairs descending pain-inhibition pathways that are important in controlling and coping with pain. Clinical trials of pharmacological and nonpharmacological therapies have shown that improving sleep quality can reduce pain and fatigue, further supporting the hypothesis that sleep dysfunction is a pathogenic stimulus of fibromyalgia.

Choy, E. H. S. *Nat. Rev. Rheumatol*. **11**, 513–520 (2015); published online 28 April 2015; doi:10.1038/nrrhuem.2015.56

Introduction

Fibromyalgia is a controversial condition.[1] Some regard the diagnosis of fibromyalgia as the "medicalization of misery",[2] as neither a specific pathology nor appropriate diagnostic tests exist. No musculoskeletal condition seems to generate more frustration for patients and physicians alike. Yet, with a prevalence of 2% worldwide,[3,4] fibromyalgia is one of the most common musculoskeletal conditions. The disease is characterized by chronic widespread pain and a range of symptoms, including nonrefreshing sleep, fatigue, functional impairment, cognitive dysfunction, depression, stiffness and variable gastrointestinal symptoms, including diarrhoea and constipation. Fibromyalgia also confers a substantial economic strain on the health-care system. In studies performed in the past decade in Europe and the USA, the annual direct medical cost of fibromyalgia was €5,241 and US$9,573 per patient, respectively.[5,6] The main component of direct medical expense is referral to secondary care and diagnostic investigations, owing in part to the fact that patients with fibromyalgia are more likely to be referred to hospital specialists and have diagnostic tests than patients without fibromyalgia. A UK study showed that health-care utilization by patients with fibromyalgia is already increased compared with patients without fibromyalgia up to 10 years prior to diagnosis.[7] After diagnosis of fibromyalgia, health-care utilization declines, with fewer visits to clinics and fewer investigations.[7] In 2008, a letter from the Chief Medical Officer of the UK to all UK doctors emphasized the health-care burden of chronic widespread pain, urging for more research and declaring that information is essential to address the problem and improve outcomes for patients.[8] In this Review, advances in the understanding of the pathophysiology of fibromyalgia are discussed, with a focus on the role of sleep and pain processing.

Section of Rheumatology, Institute of Infection and Immunity, Cardiff University School of Medicine, Tenovus Building, Heath Park, Cardiff CF14 4XN, UK.
choyeh@cardiff.ac.uk

Competing interests
The author declares that he has served as a member of advisory boards, as a consultant and as a speaker for Eli Lilly, Jazz Pharmaceuticals, Pierre Fabre Medicament, Pfizer and UCB.

Clinical features of fibromyalgia

Patients with fibromyalgia have generalized pain, although the severity and anatomical location of pain can vary from day to day. Pain in response to a 'light touch' is one of the major characteristics of the disease. This feature is a clinical manifestation of allodynia (pain induced by normally innocuous stimuli), which is associated with abnormal pain processing and central sensitization. Other common symptoms of fibromyalgia are fatigue (which affects >70% of patients with fibromyalgia, as reported in patient questionnaires) and nonrestorative sleep.[9–11] Patients with fibromyalgia often complain of feeling tired and not refreshed upon waking in the morning.[12] Although some patients have difficulty in getting to sleep, many do not experience insomnia—they sleep through the night, but still feel tired in the morning.[12] Indeed, daytime somnolence is not uncommon. A history of depression is common in patients with fibromyalgia, with a lifetime prevalence of 62–86%,[13] although the frequency of current depression is lower (29–70%),[13] varying according to the criteria

Key points

- Abnormal pain processing is an important pathophysiological feature of fibromyalgia, and nonrestorative sleep is a common clinical and diagnostic feature
- Polysomnography has demonstrated that patients with fibromyalgia have reduced slow-wave sleep and α-intrusion (α-waves during non-REM [rapid eye movement]), although these sleep disturbances are not unique to fibromyalgia
- In healthy individuals. sleep deprivation can induce fibromyalgia-like symptoms and is associated with impairment in descending pain modulation
- Population studies implicate poor-quality sleep as a risk factor for the development of widespread pain, and sleep disturbances can cause depression
- Sleep dysfunction might have bidirectional roles in the pathophysiology of fibromyalgia

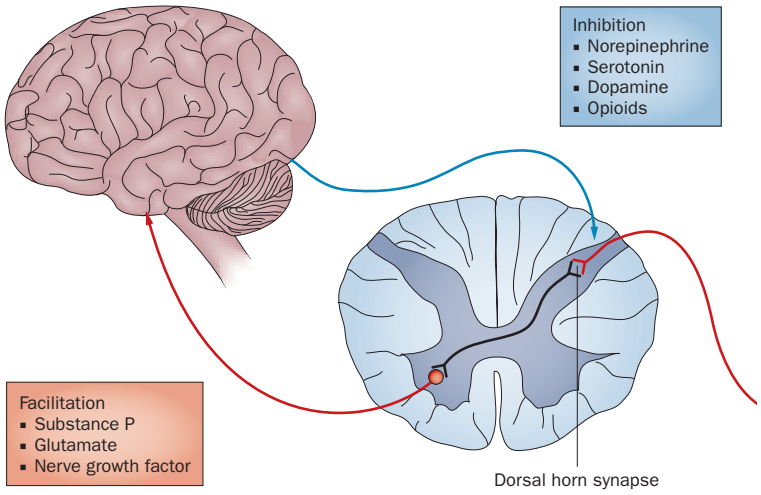

Figure 1 | Nociceptive pathways in the dorsal horn. Facilitation and inhibition by different neurotransmitters.

used to define depression. Some studies used clinical diagnostic criteria whereas others used questionnaires such as Hospital Anxiety and Depression Score (HADS). With the latter, studies have used different thresholds to define depression.

Pathophysiology of fibromyalgia

Abnormal pain processing

Although the pathogenesis of fibromyalgia is unclear, abnormal pain processing seems to be the dominant pathophysiology.[14] Pain is a complex and dynamic process, the main function of which is to protect from harm and injury by modulating behaviour. Without pain, we are susceptible to excessive tissue damage, as exemplified by patients with nerve loss such as those with neuropathic (Charcot) joints. Acute pain causes stress[15] and unpleasant emotive responses.[16]

Many studies have shown that patients with fibromyalgia have abnormal pain processing.[17–22] Tenderness due to allodynia and hyperalgesia (increased sensitivity to painful stimuli) indicate a lowered pressure-pain threshold.[23] Dysfunctional central pain processing in patients with fibromyalgia was confirmed objectively by neuroimaging with functional MRI (fMRI), showing identical brain activation in patients with fibromyalgia and healthy individuals, but substantially less pressure was required to elicit the same pain-induced neural activity in those with fibromyalgia.[24] In parallel, patients with fibromyalgia had more neural activation (including the somatosensory cortex) than healthy individuals for any given pressure stimulus. These abnormalities have been attributed to central sensitization,[25,26] loosely defined as an increased response to stimulation mediated by amplification of signalling in the central nervous system (CNS).[27] Physiologically, central sensitization promotes behaviours that protect and immobilize injured tissues to maximize healing.[28,29] However, abnormal central sensitization can cause chronic maladaptive pain whereby the severity of pain is disproportionate to the actual tissue damage, and pain can persist after the tissues have healed, making pain itself become an illness.[30]

Abnormal ascending pain pathways

In the dorsal horn of the spinal cord, primary afferent neurons carrying nociceptive stimuli from the periphery form synapses with second-order neurons that project centrally (Figure 1). Neurotransmitters involved in this process include glutamate, substance P and nerve growth factor (NGF).[29] Increased concentrations of these neurotransmitters have been measured in spinal fluid from patients with fibromyalgia.[31–34] Interestingly, a study using proton magnetic resonance spectroscopy found that patients with fibromyalgia and high pressure-pain sensitivity had high levels of glutamate in the posterior insula compared with healthy individuals (8.09 ± 0.72 versus 6.82 ± 1.29 arbitrary units, respectively; $P = 0.009$).[35] As these neurotransmitters can increase the excitability of spinal cord neurons,[20] they are implicated in central sensitization in fibromyalgia.

Ascending neurons from the spinal cord conduct nociceptive impulses to the thalamus and then to the somatosensory cortex, where pain perception occurs. Efferent neurons also project to the amygdala and hypothalamus, which are responsible for emotive and stress responses to pain, respectively.[36] Abnormalities in these higher brain regions, including decreased cortical grey-matter density, have been detected in patients with fibromyalgia by use of modern neuroimaging techniques such as fMRI and single-photon emission CT.[37–44]

Abnormal descending inhibitory pain pathways

Descending pathways modulate pain perception from the higher brain centres.[45,46] Two main descending pathways originate in the medulla and upper brainstem, respectively. The medial pathway originates from serotonergic (5-hydroxytryptamine [5-HT]-containing) as well as glutamate-containing and γ aminobutyric acid (GABA)-containing neurons in the rostral ventromedial medulla (RVM) and nucleus raphe magnus (Figure 2).[45] The lateral pathway originates from norepinephrine-containing neurons in the dorsolateral pontine tegmentum (DLPT).[34,35] Descending neurons in both the RVM and DLPT synapse in the spinal cord and inhibit pain transmission in the dorsal horn. Evidence for

dysfunctional descending inhibitory pathways includes decreased levels of 5-HT and norepinephrine in the spinal fluid of patients with fibromyalgia.[47] Hence, both 5-HT and norepinephrine have been implicated in the pathophysiology of central sensitization in fibromyalgia. Modulation of 5-HT and norepinephrine pathways has been suggested to be a key mode of action of antidepressants, especially serotonin–norepinephrine reuptake inhibitors (SNRIs) such as duloxetine.

fMRI has shown that, compared with age-matched controls, patients with fibromyalgia have a lower pressure-pain threshold but no difference in activity in brain regions relating to attention and mood. However, the rostral anterior cingulate cortex (rACC), a region of the brain linked to the descending pain inhibitory pathways, has reduced activity in response to pain provocation in these patients, suggesting impairment of pain inhibition (Figure 3).[48] The rACC expresses high levels of μ-opioid receptors.[49] Interestingly, a study using PET found that the binding potential of μ-opioid receptors was reduced in several areas of the brain, including the rACC, in patients with fibromyalgia compared with healthy individuals.[50] Endogenous opioids and opioid receptors are important for pain modulation. These studies provide objective evidence that pain modulation is impaired in patients with fibromyalgia and might explain their poor therapeutic response to opioids.[51]

A third descending pain-modulating pathway, inhibitory conditioned pain modulation (ICPM), involves a region of the subnucleus reticularis dorsalis (SRD) in the caudal medulla.[52,53] This region is responsible for heterotopic noxious conditioning, a mechanism whereby wide-ranging neuronal activation from remote areas of the body can reduce pain from a noxious stimulus so that one pain can reduce another pain.[53] This system is distinct from the aforementioned descending pain inhibitory pathways. Abnormal ICPM processing has been shown in patients with fibromyalgia;[54–57] however, descending pain inhibiting pathways partially overlap with pain-facilitating pathways, a process thought to be involved in promoting rest and recuperation.[58–60] Abnormal pain facilitation causes central sensitization in animal models of chronic pain,[45] but whether increased pain facilitation or deficits in pain inhibition are more important in the pathogenesis of fibromyalgia remains unclear.

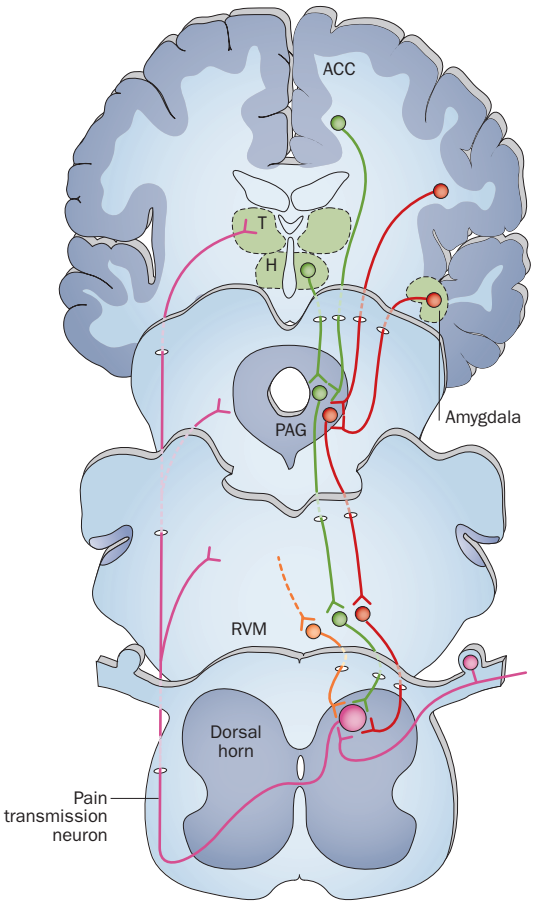

Figure 2 | Centres in the brain involved in descending inhibitory pathways. This pathway can exert both inhibitory (green) and facilitatory (red) control. A separate control channel through serotonergic neurons in the RVM (orange) can also modulate pain in a state-dependent manner. Abbreviations: ACC, anterior cingulate cortex; H, hypothalamus; PAG, periaqueductal grey; RVM, rostral ventromedial medulla; T, thalamus. Image adapted from Fields, H. State-dependent opioid control of pain. *Nat. Rev. Neurosci.* **5**, 565–575 (2004),[103] Macmillan Publishers Limited.

Sleep disturbance in fibromyalgia

Sleep disturbance is common in patients with fibromyalgia, affecting >90% of patients.[61–64] Common complaints include nocturnal restlessness, involuntary leg movements, frequent awakenings and a perception that sleep is light and nonrefreshing, with fatigue and stiffness upon awakening. Sleep disturbance correlates with pain severity and number of tender points.[65]

Several prospective studies have found correlations between poor sleep quality and worsening symptoms of fibromyalgia.[61,66,67] A path analysis found that a night of disturbed sleep was associated with increased pain, worsened physical functioning and subsequent mood disturbances.[64] In another study, poor sleep quality was shown to increase the effect of pain on fatigue.[11] A prospective study found that duration and quality of sleep were associated with depression and fatigue (as assessed by numeric rating scale), even after adjustment for the effects of positive and negative events, as well as pain, on daily mood scores.[66] Indeed, poor-quality sleep has a cumulative effect on depression.[64]

Sleep is divided into rapid-eye-movement (REM) and non-REM (NREM) stages. The latter is further divided into four stages: light (stage 1), intermediate (stage 2) and slow-wave sleep (SWS; stages 3 and 4). Approximately 25% of sleep is spent in REM, 50% in stages 1 and 2, and 20% in SWS, with only around 5% spent in wakefulness (Box 1).[68] SWS is thought to be essential to restoration (Box 1), as heart rate, blood pressure, sympathetic activity, cerebral glucose consumption and cortisol levels are decreased while growth hormone is released during this stage of sleep (Figure 4).

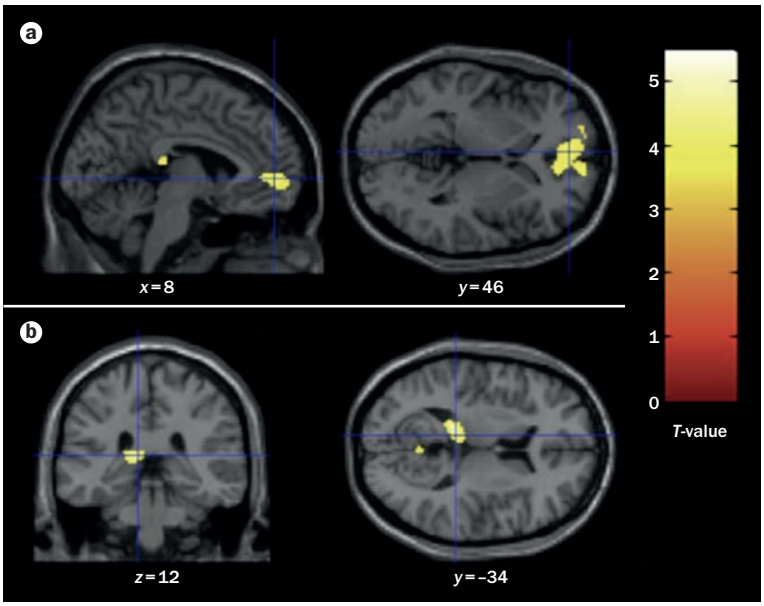

Figure 3 | Regions of the brain in which healthy individuals have more activity than patients with fibromyalgia. Functional MRI of the brain during subjectively calibrated painful stimulation subtracting sensory stimulation. Clusters correspond to **a** | the rACC, and **b** | the pulvinar nucleus of thalamus. The exact anatomical locations (*x*, *y*, *z*) are given in MNI coordinates. Abbreviations: MNI, Montreal Neurological Institute and Hospital coordinate system; rACC, rostral anterior cingulate cortex. Reproduced with permission from Wolters Kluwer Health, Inc. Jensen, K. *et al*. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain* **144**, 95–100 (2009).[48]

Box 1 | Glossary of terms

- Central sensitization: loosely defined as an increased response to stimulation that is mediated by amplification of signalling in the central nervous system
- Homeostatic sleep: the pressure to sleep and period of sleep is dependent on the length of the waking period
- Maladaptive pain: expression of alterations (plasticity) within the nociceptive system that include ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity and formation of new synaptic circuits, all of which potentially lead to disease
- Sleep restoration theory: the restoration theory states that sleep is important in restoring the ability of the body to function
- Wakefulness: daily recurring brain status and state of consciousness in which an individual is conscious and engages in coherent cognitive and behavioural responses to the external world, such as communication, ambulation, eating and sex

Polysomnography is a multiparameter test that measures brain wave activity with electroencephalography, eye movements using electrooculography, tone of submentalis muscle using electromyography and electrocardiogram during sleep, enabling objective characterization of sleep patterns. Polysomnography has been used to study sleep disturbance in patients with fibromyalgia, and the findings are discussed in the rest of this section.

Reduced slow-wave sleep

Several studies have found that SWS is reduced in patients with fibromyalgia compared with healthy individuals.[69–71] SWS duration is homeostatically regulated to be directly correlated with the duration of prior waking. Extended wakefulness will extend SWS, whereas daytime napping results in a shortened SWS.[72] Hence, decreased SWS in fibromyalgia has been suggested to be indicative of an impairment of the homeostatic drive.

α-Intrusion

α-Intrusion is the term often used to describe the prominent α-frequency (7–12 Hz) rhythm that has been observed in patients with fibromyalgia during NREM sleep.[73–76] α-Rhythms in the occipital region are associated with wakefulness in healthy individuals; however, α-rhythms in patients with fibromyalgia are localized in the frontal area of the brain.[11,77] α-Intrusion overlaid upon the δ slow-waves of SWS has been labelled as α-δ sleep.[78] Although many studies have found increased α-intrusion during NREM sleep in patients with fibromyalgia,[67,69–74] this increase is not universal.[69] α-Intrusions have been hypothesized to represent an arousal or awakening state.[67,70] α-Intrusion is not unique to fibromyalgia and has also been detected in patients with primary insomnia.[74]

Other sleep abnormalities

Reduction in stage 2 sleep spindles,[79] shorter duration of stage 2 sleep periods,[80] increased frequency of stage shifts,[81,82] and more cyclical alternating pattern of stages[83] have also been observed in patients with fibromyalgia. The significance of these features to the pathophysiology of fibromyalgia has not yet been established.[84]

Connecting sleep, pain and mood

Although the association between poor-quality sleep and fibromyalgia has been known for many years, sleep disruption had been assumed to be the result of severe pain. The potential role of sleep disruption in the causation of fibromyalgia had not been appreciated until Moldofsky and colleagues first showed that experimental sleep disturbance induced fibromyalgia-like myalgia and tenderness in healthy individuals.[85] Using auditory stimuli to interrupt SWS, Moldofsky *et al.*[85] induced myalgia, fatigue and increased tenderness with a reduced pressure-pain threshold. Subsequent research confirmed that sleep deprivation or disruption can cause increased pain severity and decreased pain threshold.[86–89]

Two epidemiological studies have examined whether poor sleep quality predisposes individuals to the development of fibromyalgia. A Norwegian study of 12,350 women who did not have musculoskeletal pain or physical disability at the time of recruitment found that 327 subsequently developed fibromyalgia over a 10-year period.[90] A dose-dependent association was found between poor sleep quality and the risk of fibromyalgia. However, the study has been criticized for not including detailed psychosocial assessment, and the case definition of fibromyalgia was based on 10-year patient recall if a doctor had ever diagnosed fibromyalgia.[91] A UK population-based epidemiological study recruited 4,326 subjects aged >50 years; 1,562 reported no pain at baseline and 2,764 reported some pain at baseline.[92] After 10 years, 800 participants (18.5%) developed widespread pain. In participants who

reported no pain at baseline, 7.7% developed widespread pain. In those who reported some pain at baseline, 24.6% developed widespread pain. In this study, mental health and social participation were assessed by HADS and Keele assessment of participation, respectively. Multivariate analysis found that age, baseline pain status, anxiety, physical health-related quality of life, cognitive impairment and nonrestorative sleep were all associated with the development of widespread pain. Of these factors, nonrestorative sleep was the strongest predictor of subsequent development of widespread pain. An experimental study randomly allocated healthy young adults to one of four groups: exercise cessation, sleep restriction (6 hours per night), both, or neither for 10 days.[93] This study confirmed a previous observation that sleep restriction is a potent contributor to the development of somatic symptoms,[67] whereas exercise is less important. This effect was especially prominent in women, who were more likely to develop somatic symptoms than men.[92]

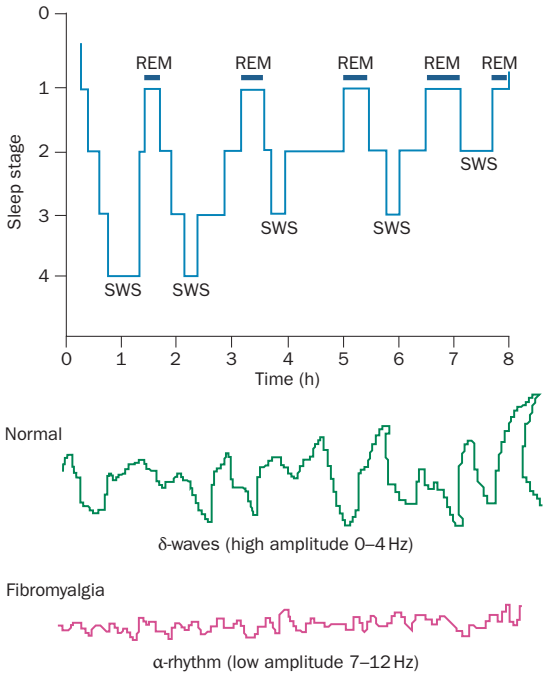

Figure 4 | Sleep cycles in a healthy individual with high-amplitude, low-frequency δ-waves during stage 3 and 4 SWS. In patients with fibromyalgia, low-amplitude high frequency α-rhythms 'intrude' on the δ-rhythm. Abbreviations: REM, rapid eye movement; SWS, slow-wave sleep.

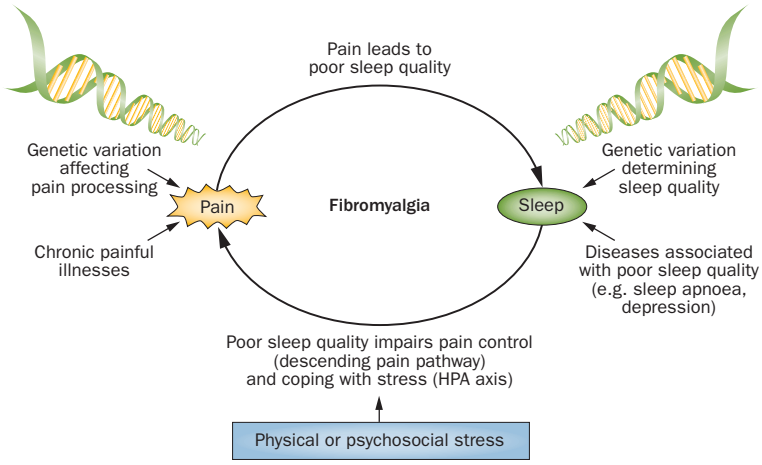

Figure 5 | Hypothesis of the role of sleep in the pathogenesis of fibromyalgia. In this model, a bidirectional relationship between sleep and pain creates a vicious cycle that can lead to fibromyalgia. Abbreviation: HPA, hypothalamic–pituitary–adrenal axis.

Several studies have shown that sleep has an important role in pain processing. Disruption of sleep in normal healthy individuals can reduce activity in descending inhibitory pain pathways,[86–88,91] whereas sleep deprivation in a population of middle-aged sedentary women resulted in impairment in ICPM similar to that observed in patients with fibromyalgia.[86] As ICPM has also been associated with anxiety and depression, a study compared the perception of experimentally-induced pain by patients with fibromyalgia and healthy controls; anxiety, depression, sleep and fibromyalgia symptoms were also measured. Sleep quality (as measured by the Pittsburgh Sleep Quality Index) was the only factor significantly correlated with reduced ICPM efficacy in patients with fibromyalgia ($r = 0.382$, $P = 0.006$).[94] Conversely, recovery after sleep deprivation, with an increase in SWS, normalized the pain threshold and reduced tenderness. Increased synaptic transmission is a feature of central sensitization and pain augmentation. As SWS can inhibit synaptic transmission, sleep disruption with reduced SWS might impair pain inhibition, resulting in pain augmentation and central sensitization.[67,85] Interestingly, disruption of SWS leads not only to a general increase in sensitivity to painful stimuli, but also to nonpainful somatic sensation,[82] which might contribute to the polysymptomatology of fibromyalgia.

Sleep disturbance is also a common symptom of patients with depression.[95] Some studies suggest that a bidirectional relationship exists between sleep disturbance on the one hand, and anxiety and depression on the other. Data from a large population-based study in Norway suggest that poor sleep quality predisposes adolescents to mental illnesses,[96] but definitive evidence is lacking.[97] As fatigue and depression are common features of fibromyalgia, fatigue and sleep disturbance might be caused by depression. However, although patients with fibromyalgia and depression have more severe symptoms than patients with fibromyalgia only, not all patients with fibromyalgia have current depression.[98]

Sodium oxybate, a sleep modifier licensed for the treatment of narcolepsy, has been effective in reducing pain and fatigue in patients with fibromyalgia in randomized controlled trials.[99,100] A path analysis study suggested that this effect is mediated almost entirely by improvements in sleep.[101] Similarly, in a randomized control trial of cognitive behavioural therapy for insomnia in patients with fibromyalgia, treatment not only improved the quality of sleep, but also reduced pain, fatigue, pain catastrophizing, anxiety and depression, and improved daily functioning.[102]

Taken together, the studies mentioned in this Review suggest that sleep disturbance might be the consequence of pain or depression, and also that sleep disturbance can reduce the ability to cope with pain. Furthermore, the pathogenesis of fibromyalgia might be similar to oncogenesis, in which the development of the disease state (chronic maladaptive pain) is a multistep process; breakdown of several control mechanisms beyond a certain threshold might cumulatively cause fibromyalgia. In such a scenario, sleep dysfunction might combine with other risk factors in the pathogenesis of fibromyalgia.

Conclusions

Traditionally, sleep disturbance has been considered a feature of fibromyalgia that is a consequence of severe pain and depression. However, both experimental and epidemiologic studies suggest that sleep dysfunction can cause fibromyalgia. Could sleep dysfunction have bidirectional roles in the pathophysiology of fibromyalgia? Is it more likely that sleep dysfunction causes fibromyalgia, or that pain and depression cause sleep dysfunction? Importantly, these pathophysiological roles need not be mutually exclusive. This factor warrants evaluation, especially in patients with early disease. Given that diagnosis of fibromyalgia is often delayed by 2–3 years,[9] by the time of diagnosis fibromyalgia is already a chronic pain state and might have been maintained by a positive feedback loop in which chronic pain or depression, or both, cause sleep disturbance and poor sleep quality impairs pain control (Figure 5). In patients with early disease, identifying those with sleep dysfunction, but without concomitant depression, could enable interventions to improve sleep quality and, therefore, possibly prevent the establishment of a vicious cycle of depression, pain and sleep dysfunction. The important roles of sleep in pain control and in the pathophysiology of fibromyalgia suggest that the development of treatments to improve sleep quality can lead to more effective management of fibromyalgia in the future.

1. Wolfe, F. Fibromyalgia wars. *J. Rheumatol.* **36**, 671–678 (2009).
2. Hadler, N. M. "Fibromyalgia" and the medicalization of misery. *J. Rheumatol.* **30**, 1668–1670 (2003).
3. Queiroz, L. P. Worldwide epidemiology of fibromyalgia. *Curr. Pain Headache Rep.* **17**, 356 (2013).
4. Wolfe, F., Ross, K., Anderson, J., Russell, I. J. & Hebert, L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. **38**, 19–28 (1995).
5. Boonen, A. *et al.* Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann. Rheum. Dis.* **64**, 396–402 (2005).
6. Centers for Disease Control and Prevention. *Fibromyalgia* [online], http://www.cdc.gov/arthritis/basics/fibromyalgia.htm (2015).
7. Hughes, G., Martinez, C., Myon, E., Taïeb, C. & Wessely, S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. *Arthritis Rheum.* **54**, 177–183 (2006).
8. Department of Health UK. *Annual report of the Chief Medical Officer on the state of public health—Pain: breaking through the barrier* [online], http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_096231.pdf (2008).
9. Choy, E. *et al.* A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Serv. Res.* **10**, 102 (2010).
10. Wolfe, F., Hawley, D. J. & Wilson, K. The prevalence and meaning of fatigue in rheumatic disease. *J. Rheumatol.* **23**, 1407–1417 (1996).
11. Nicassio, P. M., Moxham, E. G., Schuman, C. E. & Gevirtz, R. N. The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain* **100**, 271–279 (2002).
12. Kleinman, L. *et al.* Assessment of sleep in patients with fibromyalgia: qualitative development of the fibromyalgia sleep diary. *Health Qual. Life Outcomes*. **12**, 111 (2014).
13. Alciati, A., Sgiarovello, P., Atzeni, F. & Sarzi-Puttini, P. Psychiatric problems in fibromyalgia: clinical and neurobiological links between mood disorders and fibromyalgia. *Reumatismo*. **64**, 268–274 (2012).
14. Clauw, D. J. Fibromyalgia: a clinical review. *JAMA* **311**, 1547–1555 (2014).
15. Benedetti, M. *et al.* Plasma corticosterone levels in mouse models of pain. *Eur. J. Pain* **16**, 803–815 (2012).
16. Salomons, T. V., Nusslock, R., Detloff, A., Johnstone, T. & Davidson, R. J. Neural emotion regulation circuitry underlying anxiolytic effects of perceived control over pain. *J. Cogn. Neurosci.* **27**, 222–233 (2015).
17. Abeles, A. M., Pillinger, M. H., Solitar, B. M. & Abeles, M. Narrative review: the pathophysiology of fibromyalgia. *Ann. Intern. Med.* **146**, 726–734 (2007).
18. Vierck, C. J. Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain* **124**, 242–263 (2006).
19. Yunus, M. B. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin. Arthritis Rheum.* **36**, 339–356 (2007).
20. Gracely, R. H., Grant, M. A. & Giesecke, T. Evoked pain measures in fibromyalgia. *Best Pract. Res. Clin. Rheumatol.* **17**, 593–609 (2003).
21. Staud, R. & Spaeth, M. Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia. *CNS Spectr.* **13** (Suppl. 5), 12–17 (2008).
22. Granot, M. *et al.* Simultaneous recording of late and ultra-late pain evoked potentials in fibromyalgia. *Clin. Neurophysiol.* **112**, 1881–1887 (2001).
23. Lorenz, J., Grasedyck, K. & Bromm, B. Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia. *Electroencephalogr. Clin. Neurophysiol*. **100**, 165–168 (1996).
24. Gracely, R. H., Petzke, F., Wolf, J. M. & Clauw, D. J. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. **46**, 1333–1343 (2002).
25. Woolf, C. J. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* **152** (Suppl. 3), S2–S15 (2011).
26. Besson, J. M. The neurobiology of pain. *Lancet* **353**, 1610–1615 (1999).
27. Arendt-Nielsen, L. & Graven-Nielsen, T. Translational musculoskeletal pain research. *Best Pract. Res. Clin. Rheumatol.* **25**, 209–226 (2011).
28. Traub, R. J. Spinal modulation of the induction of central sensitization. *Brain Res.* **778**, 34–42 (1997).
29. Todd, A. J. & Koerber, H. R. in *Wall and Melzack's Textbook of Pain* 5th edn Ch. 4 (eds McMahon, S. B. & Koltzenburg, M.) 73–90 (Elsevier, 2006).
30. Costigan, M., Scholz, J. & Woolf, C. J. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu. Rev. Neurosci*. **32**, 1–32 (2009).
31. Vaerøy, H., Helle, R., Førre, O., Kåss, E. & Terenius, L. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain* **32**, 21–26 (1988).
32. Russell, I. J. *et al.* Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum.* **37**, 1593–1601 (1994).
33. Larson, A. A., Giovengo, S. L., Russell, I. J. & Michalek, J. E. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. *Pain* **87**, 201–211 (2000).
34. Giovengo, S. L., Russell, I. J. & Larson, A. A. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. *J. Rheumatol*. **26**, 1564–1569 (1999).
35. Harris, R. E. *et al.* Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum.* **60**, 3146–3152 (2009).
36. Bushnell, M. C. & Apkarian, A. V. in *Wall and Melzack's Textbook of Pain* 5th edn Ch. 6 (eds McMahon, S. B. & Koltzenburg, M.) 107–124 (Elsevier, 2006).
37. Bradley, L. A. *et al.* Abnormal regional cerebral blood flow in the caudate nucleus among fibromyalgia patients and non-patients is associated with insidious symptom onset. *J. Musculoskel. Pain* **7**, 285–292 (1999).
38. Mountz, J. M. *et al.* Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum*. **38**, 926–938 (1995).

39. Kuchinad, A. *et al.* Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J. Neurosci*. **27**, 4004–4007 (2007).
40. Luerding, R., Weigand, T., Bogdahn, U. & Schmidt-Wilcke, T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction. *Brain* **131**, 3222–3231 (2008).
41. Lutz, J. *et al.* White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion–tensor and volumetric imaging study. *Arthritis Rheum.* **58**, 3960–3969 (2008).
42. Sundgren, P. C. *et al.* Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. *Acad. Radiol*. **14**, 839–846 (2007).
43. Cook, D. B. *et al.* Functional imaging of pain in patients with primary fibromyalgia. *J. Rheumatol.* **31**, 364–378 (2004).
44. Kwiatek, R. *et al.* Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum.* **43**, 2823–2833 (2000).
45. Fields, H. L., Basbaum, A. I. & Heinricher, M. M. in *Wall and Melzack's Textbook of Pain* 5th edn Ch. 7 (eds McMahon, S. B. & Koltzenburg, M.) 125–142 (Elsevier, 2006).
46. Pertovaara, A. Noradrenergic pain modulation. *Prog. Neurobiol.* **80**, 53–83 (2006).
47. Russell, I. J., Vaeroy, H., Javors, M. & Nyberg, F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum*. **35**, 550–556 (1992).
48. Jensen, K. B. *et al.* Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain* **144**, 95–100 (2009).
49. Petrovic, P., Kalso, E., Petersson, K. M. & Ingvar, M. Placebo and opioid analgesia —imaging a shared neuronal network. *Science* **295**, 1737–1740 (2002).
50. Harris, R. E. *et al.* Decreased central μ-opioid receptor availability in fibromyalgia. *J. Neurosci.* **27**, 10000–10006 (2007).
51. Sörensen, J., Bengtsson, A., Bäckman, E., Henriksson, K. & Bengtsson, M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand. J. Rheumatol*. **24**, 360–365 (1995).
52. Villanueva, L. & Le Bars, D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. *Biol. Res.* **28**, 113–125 (1995).
53. Le Bars, D., Dickenson, A. H. & Besson, J. M. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain* **6**, 283–304 (1979).
54. Lautenbacher, S. & Rollman, G. B. Possible deficiencies of pain modulation in fibromyalgia. *Clin. J. Pain* **13**, 189–196 (1997).
55. Kosek, E. & Hansson, P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain* **70**, 41–51 (1997).
56. Julien, N., Goffaux, P., Arsenault, P. & Marchand, S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain* **114**, 295–302 (2005).
57. Staud, R., Robinson, M. E., Vierck, C. J. Jr & Price, D. D. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain* **101**, 167–174 (2003).
58. Le Bars, D., Gozariu, M. & Cadden, S. W. Animal models of nociception. *Pharmacol. Rev.* **53**, 597–652 (2001).
59. Vera-Portocarrero, L. P. *et al.* Descending facilitation from the rostral ventromedial medulla maintains nerve injury-induced central sensitization. *Neuroscience* **140**, 1311–1320 (2006).
60. Porreca, F., Ossipov, M. H. & Gebhart, G. F. Chronic pain and medullary descending facilitation. *Trends Neurosci.* **25**, 319–325 (2002).
61. Bigatti, S. M., Hernandez, A. M., Cronan, T. A. & Rand, K. L. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum.* **59**, 961–967 (2008).
62. Russell, I. J. & Bieber, C. S. in *Wall and Melzack's Textbook of Pain* 5th edn Ch. 44 (eds McMahon, S. B. & Koltzenburg, M.) 669–682 (Elsevier, 2006).
63. Moldofsky, H. The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. *Joint Bone Spine* **75**, 397–402 (2008).
64. Yunus, M. B., Ahles, T. A., Aldag, J. C. & Masi, A. T. Relationship of clinical features with psychological status in primary fibromyalgia. *Arthritis Rheum.* **34**, 15–21 (1991).
65. Hauri, P. & Hawkins, D. R. Alpha-delta sleep. *Electroencephalogr. Clin. Neurophysiol.* **34**, 233–237 (1973).
66. Hamilton, N. A. *et al.* Fibromyalgia: the role of sleep in affect and in negative event reactivity and recovery. *Health Psychol.* **27**, 490–497 (2008).
67. Lentz, M. J., Landis, C. A., Rothermel, J. & Shaver, J. L. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. *J. Rheumatol.* **26**, 1586–1592 (1999).
68. Scheuler, W., Stinshoff, D. & Kubicki, S. The alpha-sleep pattern. Differentiation from other sleep patterns and effect of hypnotics. *Neuropsychobiology* **10**, 183–189 (1983).
69. Anch, A. M., Lue, F. A., MacLean, A. W. & Moldofsky, H. Sleep physiology and psychological aspects of the fibrositis (fibromyalgia) syndrome. *Can. J. Psychol.* **45**, 179–184 (1991).
70. Sergi, M. *et al.* Periodic breathing during sleep in patients affected by fibromyalgia syndrome. *Eur. Respir. J.* **14**, 203–208 (1999).
71. Tononi, G. Slow wave homeostasis and synaptic plasticity. *J. Clin. Sleep Med.* **5** (Suppl. 2), S16–S19 (2009).
72. Dijk, D. J. Regulation and functional correlates of slow wave sleep. *J. Clin. Sleep Med.* **5** (Suppl. 2), S6–S15 (2009).
73. Roizenblatt, S., Moldofsky, H., Benedito-Silva, A. A. & Tufik, S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum.* **44**, 222–230 (2001).
74. Cantero, J. L., Atienza, M. & Salas, R. M. Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band. *Neurophysiol. Clin.* **32**, 54–71 (2002).
75. Van Cauter, E. *et al.* Reciprocal interactions between the GH axis and sleep. *Growth Horm. IGF Res.* **14** (Suppl. A), S10–S17 (2004).
76. Drewes, A. M. *et al.* Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. *Br. J. Rheumatol.* **34**, 629–635 (1995).
77. Horne, J. A. & Shackell, B. S. Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. *Electroencephalogr. Clin. Neurophysiol.* **79**, 271–276 (1991).
78. Branco, J., Atalaia, A. & Paiva, T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. *J. Rheumatol.* **21**, 1113–1117 (1994).
79. Landis, C. A., Lentz, M. J., Rothermel, J., Buchwald, D. & Shaver, J. L. Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain. *Sleep* **27**, 741–750 (2004).
80. Burns, J. W., Crofford, L. J. & Chervin, R. D. Sleep stage dynamics in fibromyalgia patients and controls. *Sleep Med.* **9**, 689–696 (2008).
81. Chervin, R. D. *et al.* Objective measures of disordered sleep in fibromyalgia. *J. Rheumatol.* **36**, 2009–2016 (2009).
82. Larsen, L. H., Moe, K. E., Vitiello, M. V. & Prinz, P. N. A note on the night-to-night stability of stages 3 + 4 sleep in healthy older adults: a comparison of visual and spectral evaluations of stages 3 + 4 sleep. *Sleep* **18**, 7–10 (1995).
83. Rizzi, M. *et al.* Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? *J. Rheumatol*. **31**, 1193–1199 (2004).
84. Van Cauter, E., Spiegel, K., Tasali, E. & Leproult, R. Metabolic consequences of sleep and sleep loss. *Sleep Med.* **9** (Suppl. 1), S23–S28 (2008).
85. Moldofsky, H. & Scarisbrick, P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom. Med*. **38**, 35–44 (1976).
86. Smith, M. T., Edwards, R. R., McCann, U. D. & Haythornthwaite, J. A. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* **30**, 494–505 (2007).
87. Onen, S. H., 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.* **10**, 35–42 (2001).
88. Roehrs, T., Hyde, M., Blaisdell, B., Greenwald, M. & Roth, T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* **29**, 145–151 (2006).
89. Kundermann, B., Spernal, J., Huber, M. T., Krieg, J. C. & Lautenbacher, S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom. Med.* **66**, 932–937 (2004).
90. Mork, P. J. & Nilsen, T. I. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis Rheum.* **64**, 281–284 (2012).
91. Wolfe, F. Sleep problems and risk of fibromyalgia—untenable conclusions: comment on the article by Mork *et al. Arthritis Rheum.* **64**, 1692–1693 (2012).
92. McBeth, J., Lacey, R. J. & Wilkie, R. Predictors of new-onset widespread pain in older adults: results from a population-based prospective cohort study in the UK. *Arthritis Rheumatol.* **66**, 757–767 (2014).
93. Ablin, J. N. *et al.* Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. *Clin. Exp. Rheumatol.* **31** (Suppl. 79), S53–S59 (2013).
94. Paul-Savoie, E. *et al.* Is the deficit in pain inhibition in fibromyalgia influenced by sleep impairments? *Open Rheumatol. J.* **6**, 296–302 (2012).

95. Luca, A., Luca, M. & Calandra, C. Sleep disorders and depression: brief review of the literature, case report, and nonpharmacologic interventions for depression. *Clin. Interv. Aging* **8**, 1033–1039 (2013).
96. Sivertsen, B., Harvey, A. G., Pallesen, S. & Hysing, M. Mental health problems in adolescents with delayed sleep phase: results from a large population-based study in Norway. *J. Sleep Res.* **24**, 11–18 (2014).
97. Alvaro, P. K., Roberts, R. M. & Harris, J. K. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* **36**, 1059–1068 (2013).
98. Toussaint, L. L., Vincent, A., McAllister, S. J., Oh, T. H. & Hassett, A. L. A comparison of fibromyalgia symptoms in patients with healthy versus depressive, low and reactive affect balance styles. *Scand. J. Pain* **5**, 161–166 (2014).
99. Russell, I. J., Perkins, A. T., Michalek, J. E. & Oxybate SXB-26 Fibromyalgia Syndrome Study Group. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum*. **60**, 299–309 (2009).
100. Spaeth, M. *et al.* Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. *Ann. Rheum. Dis*. **71**, 935–942 (2012).
101. Ibrahim, F., Lai, C. & Choy, E. Use of path analysis to evaluate the effects of sodium oxybate on pain reduction in patients with fibromyalgia [abstract 819]. *Arthritis Rheum*. **61** (Suppl. 10), 819 (2010).
102. Martínez, M. P. *et al.* Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. *J. Behav. Med.* **37**, 683–697 (2014).
103. Fields, H. State-dependent opioid control of pain. *Nat. Rev. Neurosci*. **5**, 565–575 (2004).