Sleep and Pain: Relationship, Mechanisms, and Managing Sleep Disturbance in the Chronic Pain Population

Janannii Selvanathan, MSc[1,2], Nicole K Y Tang, DPhil[3], Philip W H Peng, MBBS[1], Frances Chung, MBBS[1,2]

From the

1. Department of Anesthesia and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada
2. Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Ontario, Canada
3. Department of Psychology, University of Warwick, Coventry, United Kingdom

Address correspondence to:

Frances Chung, MBBS
Toronto Western Hospital
Department of Anesthesia, MCL 2-405
399 Bathurst St
Toronto, ON M5T 2S8
Email: frances.chung@uhn.ca
Phone: 416-603-4253

Running Head:

Relationship between Sleep and Pain

Conflicts of Interest:

FC reports research support from University Health Network Foundation, Up-to-date royalties, consultant to Takeda Pharma. STOP-Bang proprietary to University Health Network. NKYT received research funding as principal investigator and co-investigator from the National Institute for Health Research and the Medical Research Council. JS and PWHP did not report conflicts of interest.

Funding:

Supported by funding from ResMed Research Chair of Anesthesia, Sleep, and Perioperative Medicine, and University Health Network Foundation.

Abbreviations:

CBT-I, cognitive behavioral therapy for insomnia; CBT-P, cognitive behavioral therapy for pain; RCT, randomized controlled trial

Abstract

It is well established that sleep and pain are associated in a bidirectional manner, with more recent research suggesting a stronger influence of sleep on pain than vice versa. The present review summarizes and critically evaluates the existing literature on the relationship between sleep and pain. Observational and experimental studies will be discussed to examine the temporal links between sleep and pain. These studies provide evidence that sleep disturbance could increase the risk of developing painful conditions or maintain existing chronic pain. Conversely, good sleep quality is associated with better musculoskeletal health. Several mechanisms may underlie the association between sleep and pain, including dopaminergic signalling, opioidergic signalling, inflammation, central pain modulation, mood and negative affect, and pain-related beliefs and coping behaviors. Moreover, future directions for managing sleep disturbance in patients with chronic pain will be explored. Developing hybrid interventions that target both sleep disturbance and pain could assist in improving health outcomes and providing coordinated care.

Keywords: sleep disturbance; insomnia; pain; chronic pain; mechanisms

Introduction

Sleep is a vital and ubiquitous process that is essential for optimal bodily functioning and overall health (Luyster 2012). Despite the need for good quality sleep, non-restorative or reduced sleep has become an increasingly global issue (Stranges 2012). Several observational and experimental studies have shown the impact of sleep disturbance on pain processing and perception (Finan 2014, Lautenbacher 2006). Long-term dysregulation of the "pain system" could lead to chronic pain, which is characterized by pain persisting for three months or longer (Nicholas *et al*., 2019). Prior studies on the prevalence of insomnia in the chronic pain population showed a range from 25% to 73% (Sun 2021 and Kalmbach *et al*., 2016). These differences in point estimates among studies may be attributable to methodological heterogeneity such as differences in study samples, participant criteria, and various insomnia assessments. The prevalence of sleep disturbance may be higher in chronic pain samples than other chronic illnesses (e.g., asthma or diabetes) (Koyanagi et al., 2014), and patients with chronic pain report more sleep problems (49%) than people without chronic pain (17%) (Taylor et al., 2007). Further, the prevalence of chronic pain may be as high as 50% in individuals with chronic insomnia versus 18% in those without insomnia (Taylor 2007).

It is widely established that sleep and pain are reciprocally associated, such that pain could lead to sleep disturbance and sleep loss could exacerbate pain (Finan 2014). While previous reviews have summarized the literature on the bidirectionality of this relationship (Finan 2014, Anderson 2018, Smith 2004, Bjurstrom 2016, Lautenbacher 2006), there is some inconsistency on the included studies. Recent studies have begun to investigate the mechanisms underlying the sleep-pain association and treatment options for sleep disturbance

in the context of pain. The objectives of the present review sought to 1) discuss the current literature on the sleep-pain interaction and its bidirectionality; 2) summarize findings on the mechanisms contributing to the relationship between sleep and pain; and 3) describe the use of hybrid interventions to target sleep disturbance and pain in patients with chronic pain.

Relationship between Sleep and Pain

Observational and Experimental Research

It is widely established that the relationship between sleep and pain is bidirectional, such that pain negatively impacts sleep and sleep disruption can exacerbate pain. Table 1 showed the micro-longitudinal and longitudinal studies investigating the sleep-pain relationship. In a 1-year longitudinal population study, pain symptoms increase the risk of developing insomnia, and conversely, insomnia was a significant predictor of persistent pain (Jansson 2012). Similarly, a population-based cohort study found that total sleep time (< 6 or ≥ 9 hours) was predictive of pain frequency and more pain the next day, and pain predicted subsequent sleep duration (Edwards 2008). In patients with major burn injury, having insomnia at discharge was associated with more pain two years later, and greater levels of pain were predictive of sleep onset insomnia (Smith 2008).

The relationship between sleep and pain appears to be dose-dependent (Mork, Wiklund, Pan, Odegard 2013, Tang 2015). A 11-year cohort study of older adults found a dose-dependent and reciprocal relationship between sleep disturbance and persistent pain severity and number of pain sites (Pan 2020). Similarly, a 11-year study of 19,271 adults found an increased risk of insomnia in those with headaches lasting ≥ 7 days per month (odds ratio = 2.2)

versus those with headaches of lower frequency (Odegard 2013). Another cohort study of 6,676 older adults found the risk of insomnia three years later was greatest in individuals reporting widespread pain (odds ratio = 2.31) versus those having some (odds ratio = 1.57) or no pain at baseline (Tang 2015).

A growing body of literature suggests that sleep disturbance may predict pain to a greater extent than pain predicts sleep disturbance (**Table 1**). Sleep disturbance may increase the likelihood of the development, exacerbation, or spreading of chronic pain or painful conditions (general 2017; Aili et al., 2018; Boardman, Gupta, Mork; Pan et al., 2020; agmon 2014, lin 2017, uhlig 2018, Quartana 2010, Nitter et al., 2012; Jones 2009; Wiklund et al., 2020, skarpsno 2021). At a 1-year follow-up visit, patients with fibromyalgia reported that poorer sleep quality predicted more pain, whereas pain was not related with sleep (Bigatti et al., 2008). In veterans with musculoskeletal pain, change in sleep at three months was a stronger predictor of change in pain at 12 months, than vice versa (Koffel et al., 2016). In older patients with osteoarthritis and insomnia, short-term improvements in sleep following treatment of insomnia and pain were more predictive of pain improvements at an 18-month follow-up, than vice versa (Vitiello et al., 2013). In patients with chronic non-cancer pain, sleep quality significantly predicted pain levels the next day, whereas pain did not reliably predict sleep (Tang et al., 2012). Better patient-reported sleep quality predicted less pain in the first half of the next day, which is consistent with greater physical activity (Tang & Sanborn, 2014) and physical functioning (Gerhart et al., 2017) following sleep with better quality. Overall, these studies demonstrate that sleep disturbance significantly and strongly predicts the onset or maintenance of chronic pain conditions, whereas pain does not reliably predict the risk of sleep

problems. Given that demographic characteristics, such as physical or psychological comorbidities, may influence the strength of the sleep-pain relationship, future studies should account for the confounding effects of these variables (Marr 2020, Dubrovsky 2017).

In healthy participants, experimental sleep restriction (i.e., one night sleep time reduced by 50%) can increase sensitivity to pain and spontaneous pain levels (Matre et al., 2015). In patients with rheumatoid arthritis versus healthy control subjects, four hours of continuous sleep restriction during one night led to increased patient-reported pain, fatigue, depression, and anxiety (Irwin et al., 2012). In pain-free participants, partial sleep deprivation through forced awakenings each hour increase spontaneous pain and reduce pain inhibition the next day (Smith et al., 2007). Hence, the causal effects of sleep disturbance on subsequent pain may be attributed to disruptions in sleep continuity, and treatment of sleep fragmentation could act as a viable target for managing chronic pain.

Mechanisms Underlying the Sleep-Pain Relationship

While the relationship between sleep and pain is well known, the mechanisms contributing this association are not fully understood. Current literature suggests the potential roles of dopaminergic signalling, opioidergic signalling, central pain modulation, inflammation, negative affect, and pain-related beliefs and coping behaviors (**Figure 1**). The following section will describe these factors in more detail.

Dopaminergic Signalling

Dopamine is a neurotransmitter involved in regulating sleep, arousal, and responses to rewards (Oishi 2017). While dopamine signalling is increased during wakefulness, reduction of dopamine neurotransmission promotes sleepiness (Oishi 2017). Moreover, sleep disturbance

may lead to alterations in dopamine signalling, such that dopamine receptor (D2/D3) availability is reduced following acute sleep loss (Volkow 2008, 2012). While a prior study by Volkow et al. (2008) attributed this diminished availability to increased dopamine neurotransmission, subsequent research by the group found that a downregulation of D2/D3 receptors led to lower receptor availability (Volkow 2012). Nonetheless, changes in dopamine signalling caused by sleep disturbance may affect responses to rewards and chronic pain. For instance, imaging studies of patients with fibromyalgia have shown reduced dopamine metabolism (Wood 2007), which is associated with reduced gray matter density (Wood 2009). In a rodent model, modafinil (a dopamine reuptake inhibitor) administration reversed sleep loss-induced elevations in pain sensitivity (Alexandre 2017). Hyperalgesia caused by rapid eye movement (REM) sleep loss was associated with diminished activity of dopamine D2 receptors located in the nucleus accumbens, whereas injecting a D2 agonist prevented this hyperalgesia (Sardi 2018). Additionally, certain genotypes of chemicals involved in dopamine neurotransmission, such as the enzyme catechol-*O*-methyltransferase, could be associated with lower positive affect in the presence of greater pain in patients with fibromyalgia (Finan 2010). Women with fibromyalgia and the met/met genotype of catechol-*O*-methyltransferase reported more pain during days when pain attention or catastrophizing were greater than participants with other genotypes of the enzyme (Finan 2011). These findings suggest that altered dopamine signalling as a result of sleep disturbance may influence pain processes. More research is needed to understand the roles of dopamine signalling and the reward system on the sleep-pain relationship, and whether they act as mediators or moderators for this association. These findings could help develop interventions to regulate dopamine

neurotransmission or reward system functioning, thereby mitigating the deleterious effects of sleep disturbance on pain and responses to pain flare-ups.

Opioidergic Signalling

Opioids exert their analgesic effects by activating mu-opioid receptors of the endogenous opioid system (Pasternak and Pan 2013). Patients with chronic pain have shown diminished mu-opioid activation during a painful experience in comparison to a neutral environment (Martikainen 2013). While opioids may be prescribed for non-cancer pain management, a recent meta-analysis of 96 randomized controlled trials (RCT) found significant but small associations between opioid use and improvements in chronic non-cancer pain and physical functioning versus placebo, and similar effects to non-opioid interventions (Busse *et al*., 2018). However, chronic opioid use may have adverse effects, including nausea, excessive daytime sleepiness, sleep-disordered breathing, and hyperalgesia (Busse *et al*., 2018; Tang *et al*., 2019; Mubashir 2020).

Rodent models suggest that sleep deprivation reduces the analgesic effects of mu-opioid receptor agonists (Tomim 2016). Experimentally-induced partial (50%) or total sleep deprivation in healthy participants has shown to induce hyperalgesia and dysregulate endogenous pain inhibition processes, which are mediated by endogenous opioid peptides (Roehrs 2006, Schuh-Hofer 2013). While experimental administration of 0.1 mg/kg of morphine may decrease REM and slow wave sleep in pain-free individuals (Shaw 2005), a recent meta-analysis reported that opioid therapy may lead to improvements in self-reported sleep quality in patients with chronic pain. (Tang 2019). Additionally, the immediate negative impact of

opioid therapy on sleep may not be observed by patients without adequate access to sleep monitoring instruments. Future experimental studies should increase understanding on the potential mediating role of endogenous opioid systems on the sleep-pain association, and observational studies should investigate whether opioid therapy moderates the effects of sleep disturbance on pain outcomes in patients with chronic pain.

Central Pain Modulation

Another mechanism underlying the sleep-pain relationship involves changes in central pain modulation processes. Central pain modulation is characterized by processes in the central nervous system that affect pain signal processing (Ossipov 2010). Impaired central pain modulation can result in enhanced pain facilitation (defined by temporal summation or enhanced pain perception in response to repeated exposure to painful stimuli) or decreased pain inhibition (defined as suppressed pain perception in response to repeated exposure to painful stimuli) (Ossipov 2010). Experimental studies have shown that sleep loss or disruption may elevate pain signals by increasing pain facilitation and reducing pain inhibition, tolerance, and habituation (Eichhorn 2018, Schuh-Hofer 2013, Edwards 2009, Simpson 2018, Smith 2019). Alterations in these central pain modulatory circuits have been found to increase the risk of chronic pain (Staud 2012, Lewis 2012, O'Brien 2018), suggesting that sleep disturbance in the form of sleep fragmentation or reduced sleep duration may contribute to the development of chronic pain through central pain pathways. Females may be more vulnerable to impairments in central pain modulation induced by total sleep deprivation than males (Eichhorn 2018). Further, the central pain modulatory processes underlying the relationship between sleep

disturbance (in the form of forced awakenings) and central sensitization (defined as more pain caused by an increased gain of nociceptive pathways) may differ between the sexes, whereby sleep disturbance causes hyperalgesia in males versus enhanced temporal summation in females (Smith 2019). Lower self-reported sleep quality and sleep efficiency have also been associated with impaired central pain modulatory processes in chronic pain samples (Klyne 2018, Edwards 2009). Patients with insomnia have also demonstrated decreased pain inhibition, which may indicate a "ceiling effect" on pain inhibitory processes caused by prolonged subthreshold pain (Haack 2012). Interestingly, changes in certain central pain modulation processes, specifically pain habituation, may only occur after chronic sleep deprivation, and prolonged sleep recovery may be needed to reverse these changes (Simpson 2018). Further research is needed to increase understanding on the role of central pain modulatory circuits in the sleep-pain relationship. Future studies should also determine the extent to which changes in central pain processes recover upon sleep restoration.

Inflammation

Inflammatory mechanisms may play a role in elevating the pain response following sleep deprivation. Experimental sleep loss has shown to increase levels of proinflammatory markers, such as the tumor necrosis factor alpha, C-reactive protein, and interleukins (Haack 2007, Chennaoui 2011, Meier-Ewert 2004). Indeed, a recent meta-analysis of 72 studies found that sleep disturbance, shorter sleep duration < 7 hours, and longer sleep duration > 8 hours were associated with enhanced concentration of interleukin-6, and C-reactive protein (Irwin 2016). Elevations in these markers appear to be more exacerbated in females after partial sleep

deprivation of four hours (Irwin 2010), which may contribute to the increased risk of chronic pain in females versus males (Bartley 2013). Moreover, prior research has shown significant correlations between higher levels of interleukin-6 and sleep deprivation-induced increases in pain (Haack 2007). Longitudinal research has also shown that every one-hour reductions in sleep duration is related with increased levels of C-reactive protein and interleukin-6 five years later (Ferrie 2013). These findings indicate the need for experimental trials and longitudinal studies to determine the causality of these associations and whether restoring sleep could reduce the activation of proinflammatory markers.

Depressive Symptoms, Anxiety Symptoms, and Negative Affect

Both the chronic pain and insomnia populations commonly report comorbid depressive (Kwiatkowska et al., 2019; Sivertsen et al., 2014) and anxiety symptoms (Jackson et al., 2014; Radat et al., 2013). Conversely, prior research has investigated whether sleep influences pain indirectly via psychosocial factors. For instance, depressive symptoms (Generaal 2017, Harrison et al., 2015; Nicassio et al., 2011; Parmelee et al., 2014; O'Brien 2011), negative affect (Ravyts 2018, O'Brien et al., 2010), and anxiety symptoms (Jansson-Frojmark & Boersma, 2012, Dunietz 2017) may contribute to sleep disturbance reported by patients with chronic pain, and have shown to mediate the relationship between sleep disturbance and pain outcomes (e.g., pain severity, pain interference, disability, development of chronic pain). In turn, sleep may influence the relationship between pain and depressive symptoms (Diaz-Piedra et al., 2014; Miro et al., 2011), and sleep disturbance may predict the onset of depression in patients with chronic pain (Campbell et al., 2013). Further, pain may mediate the sleep-depression

association (Hamilton et al., 2012) and depressive symptoms may also mediate the association between insomnia or short sleep duration (⩽6 hours) and chronic pain development (Generaal et al., 2016). Further, depressive symptoms have shown to be greatest in patients with poorer sleep and pain, suggesting that sleep disturbance may increase the risk of depression in patients with severe chronic pain (Parmelee 2016). While it is postulated that poorer sleep could result in decreased positive affect, there are mixed findings on whether positive affect mediates the relationship between sleep and pain (Whibley 2019, Ravyts 2019, Kothari 2015). Further studies are needed to enhance knowledge on the interrelationships between sleep, pain, and mood outcomes in adults with chronic pain. Findings from this research could assist in developing interventions that identify and target sleep disturbance and negative affect in the context of chronic pain.

Pain-Related Beliefs and Coping Behaviors

Several cognitive processes may contribute to the severity of sleep disturbance, including pain-related dysfunctional beliefs and attitudes about sleep (Afolalu et al., 2016), the belief that sleep is an "escape" from pain (Tang et al., 2009), worries about sleep (Dillon et al., 2012), and pre-sleep arousal (Smith 2001). Pain catastrophizing is the tendency to exaggerate the threat level of a painful stimulus, feel helpless, and show an inability to reduce pain-related thoughts during a painful experience (Turner 2001). Pain catastrophizing has shown to be a risk factor for sleep disturbance in patients with chronic pain, and indirectly influence pain severity and interference through sleep disturbance (Beunaver 2012). In patients with knee osteoarthritis, pain catastrophizing moderated the association between sleep efficiency and

central sensitization, such that patients with lower sleep efficiency and greater catastrophizing had increased central sensitization (Campbell 2015). Pain catastrophizing is increased in patients with both chronic pain and insomnia (MacDonald 2008). Moreover, having comorbid chronic pain and insomnia is associated with increased avoidance of cognitive tasks that were perceived to worsen symptoms or exceed the participant's mental capacity (MacDonald 2008).

Behavioral mechanisms may also play a role in sleep disturbance among patients with chronic pain. Due to their pain, patients are often underactive and report low levels of physical activity (Larsson et al., 2017). It is well established that engaging in physical activity throughout the day will elevate levels of adenosine, a sleep-promoting neurochemical, thereby increasing the pressure to fall asleep (i.e., sleep drive) and facilitating slow wave sleep at night (Dworak et al., 2007). Anticipating pain or avoiding activity can also worsen pain intensity (Kroska, 2016) and lower physical functioning (Merriwether et al., 2018). Additionally, patients may spend a significant portion of their day in a lying position to cope with their pain or fatigue, perform their daily tasks in the bedroom environment, or take naps in an attempt to "catch up on their sleep" (Raheim & Haland, 2006; Theadom & Cropley, 2010). However, these behaviors may exacerbate sleep disturbance, reduce sleep drive, and strengthen the bedroom environment as a conditioned stimulus for arousal instead of sleepiness (Edinger & Carney, 2014). Indeed, patients with chronic pain and insomnia engage in more safety-seeking behaviors than those with pain or insomnia alone (MacDonald 2008). Due to their sleep-interfering effects, these behaviors are often identified and challenged during treatment for insomnia.

Other Factors Influencing the Sleep-Pain Relationship

Other potential mediators of the sleep-pain association include fatigue (Bonvanie 2016), cortisol reactivity (Goodin 2012) and pain helplessness (Hamilton 2012). While diet and physical activity are not indicated as mediators, both factors have been related with sleep (Grandner 2014; Banno 2018) or pain (Choi 2014, Segura 2019) alone. Future studies should conclusively determine whether these factors play mediating roles on the impact of sleep disturbance on pain.

Managing Sleep Disturbance in Patients with Chronic Pain

Hybrid Interventions for Managing Sleep Disturbance and Chronic Pain

Given the prominent co-occurrence of chronic pain and sleep disturbance, an emerging trend in research is the development of hybrid programs involving cognitive behavioral therapy for insomnia (CBT-I) and chronic pain (CBT-P) (Tang 2018). CBT-I is the first-line recommended treatment for insomnia (Qaseem et al., 2016; Riemann et al., 2017), and involves a multicomponent approach to targeting cognitive and behavioral processes that contribute to persistent sleep disturbance (Edinger & Carney, 2014). Common CBT-I components include psychoeducation on sleep, relaxation training, stimulus control (instructions to strengthen the bed/bedroom as a cue for sleepiness, such as avoiding to perform wakeful activities in the bed), sleep restriction (increase the proportion of time spent in bed asleep versus awake), cognitive restructuring, and strategies to prevent relapses (Edinger & Carney, 2014). Several RCTs have investigated the effectiveness of CBT-I in patients with comorbid insomnia and chronic non-

cancer pain. In a meta-analysis of 12 RCT, Selvanathan *et al*. reported significant treatment effects on self-reported sleep questionnaires (e.g., Insomnia Severity Index, Pittsburgh Sleep Quality Index), sleep diary variables (sleep onset latency, wake after sleep onset, and sleep efficiency), pain, and depressive symptoms at post-treatment (Selvanathan et al., 2021).

Common CBT-P components include psychoeducation on pain, relaxation/mindfulness exercises, activity pacing, training to improve pain-related communication, cognitive restructuring, and coping strategies for pain flare-ups (British Pain Society, 2018). While their long-term efficacy remains unclear, CBT-P could lead to small to moderate improvements on pain interference and intensity (Williams 2020). Our recent meta-analysis demonstrated that combining CBT-I with CBT-P can lead to significant effects on pain intensity and interference at post-treatment versus control (i.e., no or passive intervention), but not at follow-up (Selvanathan *et al*., 2021). However, these effects on pain were similar to trials utilizing CBT-I alone (Selvanathan *et al*., 2021).

Evidently, future studies incorporating robust and randomized controlled designs are warranted to further investigate the effectiveness of hybrid treatments in patients with chronic pain and sleep disturbance. Future studies should utilize longer follow-up periods and compare the effects of hybrid treatments in patients with different levels of pain. Research on hybrid treatments could provide valuable insight on providing patient care through a more holistic and efficient approach, whereby multiple comorbidities can be simultaneously treated through one program (Tang *et al*., 2018). In turn, these programs can increase the accessibility of sleep and pain care by reducing wait-times and the need to obtain referrals to separate sleep or pain

management services, which can ultimately lead to enhanced, comprehensive, and coordinated patient care.

Conclusions

Sleep disturbance is a common complaint in patients with chronic pain. The relationship between sleep and pain is bidirectional, with evidence suggesting that sleep is a stronger predictor of pain than vice versa. Experimental and observational research have elucidated the potential direct (dopaminergic and opioidergic neurotransmission, central pain modulation, inflammation) or indirect (mood, pain-related beliefs and coping behaviors) mechanisms underlying the relationship between sleep and pain. In patients with chronic pain, CBT-I is an established therapy for sleep disturbance improving health outcomes beyond sleep and pain, including depressive and anxiety symptoms. Despite the growing body of literature on this topic, further research is warranted on the following areas: 1) examine longitudinal data to conclusively determine whether sleep disturbance predicts the onset and persistence of chronic pain, 2) utilize preclinical models, imaging methods, and epidemiological studies to investigate the mechanisms underlying the sleep-pain association, and 3) conduct experimental trials to assess the feasibility and efficacy of delivering CBT-I in a hybrid (e.g., CBT-I/CBT-P) format in individuals with chronic pain and sleep disturbance. Given the significant variability in sleep and pain assessments in the reviewed studies, future studies should consider the suitability of an assessment based on the aspect of sleep or pain it measures, along with the need to include self-reported and objective instruments. As chronic pain and sleep disturbance have both shown to impair overall health and increase burden on the individual and society, developing

methods to prevent and manage sleep disturbance and pain would be an important step towards addressing these global health issues.

References

1. Stranges S, Tigbe W, Gómez-Olivé FX, Thorogood M, Kandala NB. Sleep problems: an emerging global epidemic? Findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. *Sleep*. 2012;35(8):1173-1181. Published 2012 Aug 1. doi:10.5665/sleep.2012
2. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev*. 2006;10(5):357-369. doi:10.1016/j.smrv.2005.08.001
3. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain*. 2013;14(12):1539-1552. doi:10.1016/j.jpain.2013.08.007
4. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28-37. doi:10.1097/j.pain.0000000000001390
5. Kalmbach DA, Pillai V, Arnedt JT, Drake CL. DSM-5 Insomnia and Short Sleep: Comorbidity Landscape and Racial Disparities. *Sleep*. 2016;39(12):2101-2111. Published 2016 Dec 1. doi:10.5665/sleep.6306
6. Sun Y, Laksono I, Selvanathan J, et al. Prevalence of sleep disturbances in patients with chronic non-cancer pain: A systematic review and meta-analysis. *Sleep Med Rev*. 2021;57:101467. doi:10.1016/j.smrv.2021.101467
7. Koyanagi A, Garin N, Olaya B, et al. Chronic conditions and sleep problems among adults aged 50 years or over in nine countries: a multi-country study [published correction appears in PLoS One. 2015;10(9):e0138261]. *PLoS One*. 2014;9(12):e114742. Published 2014 Dec 5. doi:10.1371/journal.pone.0114742
8. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems [published correction appears in Sleep. 2007 Jul 1;30(7):table of contents]. *Sleep*. 2007;30(2):213-218. doi:10.1093/sleep/30.2.213
9. Andersen ML, Araujo P, Frange C, Tufik S. Sleep Disturbance and Pain: A Tale of Two Common Problems. *Chest*. 2018;154(5):1249-1259. doi:10.1016/j.chest.2018.07.019
10. Bjurstrom MF, Irwin MR. Polysomnographic characteristics in nonmalignant chronic pain populations: A review of controlled studies. *Sleep Med Rev*. 2016;26:74-86. doi:10.1016/j.smrv.2015.03.004
11. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*. 2004;8(2):119-132. doi:10.1016/S1087-0792(03)00044-3
12. Jansson-Fröjmark M, Boersma K. Bidirectionality between pain and insomnia symptoms: a prospective study. *Br J Health Psychol*. 2012;17(2):420-431. doi:10.1111/j.2044-8287.2011.02045.x
13. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. *Pain*. 2008;137(1):202-207. doi:10.1016/j.pain.2008.01.025
14. Smith MT, Klick B, Kozachik S, et al. Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. *Pain*. 2008;138(3):497-506. doi:10.1016/j.pain.2008.01.028

15. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis Rheum*. 2012;64(1):281-284.
16. Wiklund T, Gerdle B, Linton SJ, Dragioti E, Larsson B. Insomnia is a risk factor for spreading of chronic pain: A Swedish longitudinal population study (SwePain). *Eur J Pain*. 2020;24(7):1348-1356. doi:10.1002/ejp.1582
17. Ødegård SS, Sand T, Engstrøm M, Zwart JA, Hagen K. The impact of headache and chronic musculoskeletal complaints on the risk of insomnia: longitudinal data from the Nord-Trøndelag health study. *J Headache Pain*. 2013;14(1):24. Published 2013 Mar 12. doi:10.1186/1129-2377-14-24
18. Tang NK, McBeth J, Jordan KP, Blagojevic-Bucknall M, Croft P, Wilkie R. Impact of musculoskeletal pain on insomnia onset: a prospective cohort study. *Rheumatology (Oxford)*. 2015;54(2):248-256. doi:10.1093/rheumatology/keu283
19. Pan F, Tian J, Cicuttini F, Jones G. Sleep Disturbance and Its Association with Pain Severity and Multisite Pain: A Prospective 10.7-Year Study. *Pain Ther*. 2020;9(2):751-763. doi:10.1007/s40122-020-00208-x
20. Agmon M, Armon G. Increased insomnia symptoms predict the onset of back pain among employed adults. *PLoS One*. 2014;9(8):e103591. Published 2014 Aug 1. doi:10.1371/journal.pone.0103591
21. Aili K, Andersson M, Bremander A, Haglund E, Larsson I, Bergman S. Sleep problems and fatigue as predictors for the onset of chronic widespread pain over a 5- and 18-year perspective. *BMC Musculoskelet Disord*. 2018;19(1):390. Published 2018 Nov 3. doi:10.1186/s12891-018-2310-5
22. Boardman HF, Thomas E, Millson DS, Croft PR. The natural history of headache: predictors of onset and recovery. *Cephalalgia*. 2006;26(9):1080-1088.
23. Generaal E, Vogelzangs N, Penninx BW, Dekker J. Insomnia, Sleep Duration, Depressive Symptoms, and the Onset of Chronic Multisite Musculoskeletal Pain. *Sleep*. 2017;40(1):10.1093/sleep/zsw030. doi:10.1093/sleep/zsw030
24. Gupta A, Silman AJ, Ray D, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology (Oxford)*. 2007;46(4):666-671.
25. Lin WC, Shen CC, Tsai SJ, Yang AC. Increased Risk of Myofascial Pain Syndrome Among Patients with Insomnia. *Pain Med*. 2017;18(8):1557-1565. doi:10.1093/pm/pnw300
26. Nitter AK, Pripp AH, Forseth KØ. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. *Scand J Pain*. 2012;3(4):210-217. Published 2012 Oct 1. doi:10.1016/j.sjpain.2012.04.001
27. Quartana PJ, Wickwire EM, Klick B, Grace E, Smith MT. Naturalistic changes in insomnia symptoms and pain in temporomandibular joint disorder: a cross-lagged panel analysis. *Pain*. 2010;149(2):325-331.
28. Skarpsno ES, Nilsen TIL, Hagen K, Mork PJ. Long-term changes in self-reported sleep quality and risk of chronic musculoskeletal pain: The HUNT Study. *J Sleep Res*. 2021;e13354.
29. Uhlig BL, Sand T, Nilsen TI, Mork PJ, Hagen K. Insomnia and risk of chronic musculoskeletal complaints: longitudinal data from the HUNT study, Norway. *BMC*

Musculoskelet Disord. 2018;19(1):128. Published 2018 Apr 25. doi:10.1186/s12891-018-2035-5
30. Jones EA, McBeth J, Nicholl B, et al. What characterizes persons who do not report musculoskeletal pain? Results from a 4-year Population-based longitudinal study (the Epifund study). *J Rheumatol*. 2009;36(5):1071-1077. doi:10.3899/jrheum.080541
31. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum*. 2008;59(7):961-967. doi:10.1002/art.23828
32. Koffel E, Kroenke K, Bair MJ, Leverty D, Polusny MA, Krebs EE. The bidirectional relationship between sleep complaints and pain: Analysis of data from a randomized trial. *Health Psychol*. 2016;35(1):41-49. doi:10.1037/hea0000245
33. Vitiello MV, McCurry SM, Shortreed SM, et al. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *Pain*. 2014;155(8):1547-1554.
34. Tang NK, Goodchild CE, Sanborn AN, Howard J, Salkovskis PM. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep*. 2012;35(5):675-87A. Published 2012 May 1. doi:10.5665/sleep.1830
35. Tang NK, Sanborn AN. Better quality sleep promotes daytime physical activity in patients with chronic pain? A multilevel analysis of the within-person relationship. *PLoS One*. 2014;9(3):e92158. Published 2014 Mar 25. doi:10.1371/journal.pone.0092158
36. Gerhart JI, Burns JW, Post KM, et al. Relationships Between Sleep Quality and Pain-Related Factors for People with Chronic Low Back Pain: Tests of Reciprocal and Time of Day Effects. *Ann Behav Med*. 2017;51(3):365-375. doi:10.1007/s12160-016-9860-2
37. Marr NC, Van Liew C, Carovich TF, Cecchini GA, McKinley LE, Cronan TA. The Effects of Racial/Ethnic Minority Status on Sleep, Mood Disturbance, and Depression in People with Fibromyalgia. *Psychol Res Behav Manag*. 2020;13:343-353. Published 2020 Apr 16. doi:10.2147/PRBM.S242699
38. Dubrovsky B, Janal MN, Lavigne GJ, et al. Depressive symptoms account for differences between self-reported versus polysomnographic assessment of sleep quality in women with myofascial TMD. *J Oral Rehabil*. 2017;44(12):925-933. doi:10.1111/joor.12552
39. Dzierzewski JM, Williams JM, Roditi D, et al. Daily variations in objective nighttime sleep and subjective morning pain in older adults with insomnia: evidence of covariation over time. *J Am Geriatr Soc*. 2010;58(5):925-930.
40. Salwen JK, Smith MT, Finan PH. Mid-Treatment Sleep Duration Predicts Clinically Significant Knee Osteoarthritis Pain reduction at 6 months: Effects From a Behavioral Sleep Medicine Clinical Trial. *Sleep*. 2017;40(2):zsw064. doi:10.1093/sleep/zsw064
41. Matre D, Hu L, Viken LA, et al. Experimental Sleep Restriction Facilitates Pain and Electrically Induced Cortical Responses. *Sleep*. 2015;38(10):1607-1617. Published 2015 Oct 1. doi:10.5665/sleep.5058

42. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep*. 2012;35(4):537-543. Published 2012 Apr 1. doi:10.5665/sleep.1742
43. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep*. 2007;30(4):494-505. doi:10.1093/sleep/30.4.494
44. Oishi Y, Lazarus M. The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci Res*. 2017;118:66-73. doi:10.1016/j.neures.2017.04.008
45. Volkow ND, Wang GJ, Telang F, et al. Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. *J Neurosci*. 2008;28(34):8454-8461. doi:10.1523/JNEUROSCI.1443-08.2008
46. Volkow ND, Tomasi D, Wang GJ, et al. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. *J Neurosci*. 2012;32(19):6711-6717. doi:10.1523/JNEUROSCI.0045-12.2012
47. Wood PB, Patterson JC 2nd, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL. Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study. *J Pain*. 2007;8(1):51-58. doi:10.1016/j.jpain.2006.05.014
48. Wood PB, Glabus MF, Simpson R, Patterson JC 2nd. Changes in gray matter density in fibromyalgia: correlation with dopamine metabolism. *J Pain*. 2009;10(6):609-618. doi:10.1016/j.jpain.2008.12.008
49. Alexandre C, Latremoliere A, Ferreira A, et al. Decreased alertness due to sleep loss increases pain sensitivity in mice. *Nat Med*. 2017;23(6):768-774. doi:10.1038/nm.4329
50. Sardi NF, Tobaldini G, Morais RN, Fischer L. Nucleus accumbens mediates the pronociceptive effect of sleep deprivation: the role of adenosine A2A and dopamine D2 receptors. *Pain*. 2018;159(1):75-84. doi:10.1097/j.pain.0000000000001066
51. Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. Genetic influences on the dynamics of pain and affect in fibromyalgia [published correction appears in Health Psychol. 2010 May;29(3):245]. *Health Psychol*. 2010;29(2):134-142. doi:10.1037/a0018647
52. Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. *Pain*. 2011;152(2):300-307. doi:10.1016/j.pain.2010.10.024
53. Pasternak GW, Pan YX. Mu opioids and their receptors: evolution of a concept. *Pharmacol Rev*. 2013;65(4):1257-1317. Published 2013 Sep 27. doi:10.1124/pr.112.007138
54. Martikainen IK, Peciña M, Love TM, et al. Alterations in endogenous opioid functional measures in chronic back pain. *J Neurosci*. 2013;33(37):14729-14737. doi:10.1523/JNEUROSCI.1400-13.2013
55. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472
56. Tang NKY, Stella MT, Banks PDW, Sandhu HK, Berna C. The effect of opioid therapy on sleep quality in patients with chronic non-malignant pain: A systematic review and

exploratory meta-analysis. *Sleep Med Rev*. 2019;45:105-126. doi:10.1016/j.smrv.2019.03.005
57. Mubashir
58. Tomim DH, Pontarolla FM, Bertolini JF, et al. The Pronociceptive Effect of Paradoxical Sleep Deprivation in Rats: Evidence for a Role of Descending Pain Modulation Mechanisms. *Mol Neurobiol*. 2016;53(3):1706-1717. doi:10.1007/s12035-014-9059-0
59. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep*. 2006;29(2):145-151. doi:10.1093/sleep/29.2.145
60. Schuh-Hofer S, Wodarski R, Pfau DB, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain*. 2013;154(9):1613-1621. doi:10.1016/j.pain.2013.04.046
61. Haack M, Scott-Sutherland J, Santangelo G, Simpson NS, Sethna N, Mullington JM. Pain sensitivity and modulation in primary insomnia. *Eur J Pain*. 2012;16(4):522-533. doi:10.1016/j.ejpain.2011.07.007
62. Shaw IR, Lavigne G, Mayer P, Choinière M. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study [published correction appears in Sleep. 2006 Feb 1;29(2):136. Dosage error in published abstract; MEDLINE/PubMed abstract corrected]. *Sleep*. 2005;28(6):677-682. doi:10.1093/sleep/28.6.677
63. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest*. 2010;120(11):3779-3787. doi:10.1172/JCI43766
64. Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *Eur J Pain*. 2009;13(10):1043-1047. doi:10.1016/j.ejpain.2008.12.007
65. Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. *Neuroscience*. 2018;387:191-200. doi:10.1016/j.neuroscience.2017.09.044
66. Smith MT Jr, Remeniuk B, Finan PH, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: implications for sex differences in chronic pain. *Sleep*. 2019;42(2):zsy209. doi:10.1093/sleep/zsy209
67. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain*. 2012;13(10):936-944. doi:10.1016/j.jpain.2012.07.005
68. O'Brien AT, Deitos A, Triñanes Pego Y, Fregni F, Carrillo-de-la-Peña MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *J Pain*. 2018;19(8):819-836. doi:10.1016/j.jpain.2018.01.010
69. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother*. 2012;12(5):577-585. doi:10.1586/ern.12.41
70. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of

Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *J Pain*. 2018;19(8):942.e1-942.e18. doi:10.1016/j.jpain.2018.02.017
71. Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. *Pain*. 2018;159(1):33-40. doi:10.1097/j.pain.0000000000001053
72. Chennaoui M, Sauvet F, Drogou C, et al. Effect of one night of sleep loss on changes in tumor necrosis factor alpha (TNF-α) levels in healthy men. *Cytokine*. 2011;56(2):318-324. doi:10.1016/j.cyto.2011.06.002
73. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007;30(9):1145-1152. doi:10.1093/sleep/30.9.1145
74. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*. 2004;43(4):678-683. doi:10.1016/j.jacc.2003.07.050
75. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry*. 2016;80(1):40-52. doi:10.1016/j.biopsych.2015.05.014
76. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-58. doi:10.1093/bja/aet127
77. Ferrie JE, Kivimäki M, Akbaraly TN, et al. Associations between change in sleep duration and inflammation: findings on C-reactive protein and interleukin 6 in the Whitehall II Study. *Am J Epidemiol*. 2013;178(6):956-961. doi:10.1093/aje/kwt072
78. Kwiatkowska B, Kłak A, Raciborski F, Maślińska M. The prevalence of depression and insomnia symptoms among patients with rheumatoid arthritis and osteoarthritis in Poland: a case control study. *Psychol Health Med*. 2019;24(3):333-343. doi:10.1080/13548506.2018.1529325
79. Sivertsen B, Lallukka T, Salo P, et al. Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway. *J Sleep Res*. 2014;23(2):124-132. doi:10.1111/jsr.12102
80. Jackson ML, Sztendur EM, Diamond NT, Byles JE, Bruck D. Sleep difficulties and the development of depression and anxiety: a longitudinal study of young Australian women. *Arch Womens Ment Health*. 2014;17(3):189-198. doi:10.1007/s00737-014-0417-8
81. Radat F, Margot-Duclot A, Attal N. Psychiatric co-morbidities in patients with chronic peripheral neuropathic pain: a multicentre cohort study. *Eur J Pain*. 2013;17(10):1547-1557. doi:10.1002/j.1532-2149.2013.00334.x
82. Harrison L, Wilson S, Heron J, Stannard C, Munafò MR. Exploring the associations shared by mood, pain-related attention and pain outcomes related to sleep disturbance in a chronic pain sample. *Psychol Health*. 2016;31(5):565-577. doi:10.1080/08870446.2015.1124106
83. Nicassio PM, Ormseth SR, Kay M, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. *Pain*. 2012;153(1):107-112. doi:10.1016/j.pain.2011.09.024

84. Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis: linkages with pain, disability, and depressive symptoms. *Arthritis Care Res (Hoboken)*. 2015;67(3):358-365. doi:10.1002/acr.22459
85. O'Brien EM, Waxenberg LB, Atchison JW, et al. Negative mood mediates the effect of poor sleep on pain among chronic pain patients. *Clin J Pain*. 2010;26(4):310-319. doi:10.1097/AJP.0b013e3181c328e9
86. Ravyts SG, Dzierzewski JM, Raldiris T, Perez E. Sleep and pain interference in individuals with chronic pain in mid- to late-life: The influence of negative and positive affect. *J Sleep Res*. 2019;28(4):e12807. doi:10.1111/jsr.12807
87. Dunietz GL, Swanson LM, Jansen EC, et al. Key insomnia symptoms and incident pain in older adults: direct and mediated pathways through depression and anxiety. *Sleep*. 2018;41(9):zsy125. doi:10.1093/sleep/zsy125
88. Diaz-Piedra C, Catena A, Miro E, Martinez MP, Sanchez AI, Buela-Casal G. The impact of pain on anxiety and depression is mediated by objective and subjective sleep characteristics in fibromyalgia patients. *Clin J Pain*. 2014;30(10):852-859. doi:10.1097/AJP.0000000000000040
89. Miró E, Lupiáñez J, Martínez MP, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. *J Health Psychol*. 2011;16(5):770-782. doi:10.1177/1359105310390544
90. Campbell P, Tang N, McBeth J, et al. The role of sleep problems in the development of depression in those with persistent pain: a prospective cohort study. *Sleep*. 2013;36(11):1693-1698. Published 2013 Nov 1. doi:10.5665/sleep.3130
91. Hamilton NA, Pressman M, Lillis T, Atchley R, Karlson C, Stevens N. Evaluating Evidence for the Role of Sleep in Fibromyalgia: A Test of the Sleep and Pain Diathesis Model. *Cognit Ther Res*. 2012;36(6):806-814. doi:10.1007/s10608-011-9421-8
92. Whibley D, AlKandari N, Kristensen K, et al. Sleep and Pain: A Systematic Review of Studies of Mediation. *Clin J Pain*. 2019;35(6):544-558. doi:10.1097/AJP.0000000000000697
93. Afolalu EF, Moore C, Ramlee F, Goodchild CE, Tang NK. Development of the Pain-Related Beliefs and Attitudes about Sleep (PBAS) Scale for the Assessment and Treatment of Insomnia Comorbid with Chronic Pain. *J Clin Sleep Med*. 2016;12(9):1269-1277. Published 2016 Sep 15. doi:10.5664/jcsm.6130
94. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychol Med*. 2006;36(5):575-586. doi:10.1017/S0033291705006859
95. Dillon, H.R., Thomas, S.J. & Lichstein, K.L. Cognitive Arousal and Sleep Complaints in Chronic Pain. Cogn Ther Res 36, 149–155 (2012). https://doi.org/10.1007/s10608-011-9420-9
96. Smith MT, Perlis ML, Carmody TP, Smith MS, Giles DE. Presleep cognitions in patients with insomnia secondary to chronic pain. *J Behav Med*. 2001;24(1):93-114. doi:10.1023/a:1005690505632
97. Turner JA, Aaron LA. Pain-related catastrophizing: what is it?. *Clin J Pain*. 2001;17(1):65-71. doi:10.1097/00002508-200103000-00009

98. Buenaver LF, Quartana PJ, Grace EG, et al. Evidence for indirect effects of pain catastrophizing on clinical pain among myofascial temporomandibular disorder participants: the mediating role of sleep disturbance. *Pain*. 2012;153(6):1159-1166. doi:10.1016/j.pain.2012.01.023
99. Campbell CM, Buenaver LF, Finan P, et al. Sleep, Pain Catastrophizing, and Central Sensitization in Knee Osteoarthritis Patients With and Without Insomnia. *Arthritis Care Res (Hoboken)*. 2015;67(10):1387-1396. doi:10.1002/acr.22609
100. MacDonald S, Linton SJ, Jansson-Frojmark M. Avoidant safety behaviors and catastrophizing: shared cognitive-behavioral processes and consequences in co-morbid pain and sleep disorders. *Int J Behav Med*. 2008;15(3):201-210. doi:10.1080/10705500802222675
101. Larsson C, Ekvall Hansson E, Sundquist K, Jakobsson U. Impact of pain characteristics and fear-avoidance beliefs on physical activity levels among older adults with chronic pain: a population-based, longitudinal study. *BMC Geriatr*. 2016;16:50. Published 2016 Feb 24. doi:10.1186/s12877-016-0224-3
102. Dworak M, Diel P, Voss S, Hollmann W, Strüder HK. Intense exercise increases adenosine concentrations in rat brain: implications for a homeostatic sleep drive. *Neuroscience*. 2007;150(4):789-795. doi:10.1016/j.neuroscience.2007.09.062
103. Kroska EB. A meta-analysis of fear-avoidance and pain intensity: The paradox of chronic pain. *Scand J Pain*. 2016;13:43-58. doi:10.1016/j.sjpain.2016.06.011
104. Merriwether EN, Frey-Law LA, Rakel BA, et al. Physical activity is related to function and fatigue but not pain in women with fibromyalgia: baseline analyses from the Fibromyalgia Activity Study with TENS (FAST). *Arthritis Res Ther*. 2018;20(1):199. Published 2018 Aug 29. doi:10.1186/s13075-018-1671-3
105. Råheim M, Håland W. Lived experience of chronic pain and fibromyalgia: women's stories from daily life. *Qual Health Res*. 2006;16(6):741-761. doi:10.1177/1049732306288521
106. Theadom A, Cropley M. 'This constant being woken up is the worst thing' - experiences of sleep in fibromyalgia syndrome. *Disabil Rehabil*. 2010;32(23):1939-1947. doi:10.3109/09638281003797331
107. Edinger, J. D., & Carney, C. E. (2014). *Overcoming insomnia: a cognitive-behavioral therapy approach, therapist guide*. Oxford University Press.
108. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175
109. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675-700. doi:10.1111/jsr.12594
110. Tang NKY. Cognitive behavioural therapy in pain and psychological disorders: Towards a hybrid future. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):281-289. doi:10.1016/j.pnpbp.2017.02.023
111. Selvanathan
112. Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst*

Rev. 2020;8(8):CD007407. Published 2020 Aug 12. doi:10.1002/14651858.CD007407.pub4

113. Irwin MR, Carrillo C, Olmstead R. Sleep loss activates cellular markers of inflammation: sex differences. *Brain Behav Immun*. 2010;24(1):54-57. doi:10.1016/j.bbi.2009.06.001

114. Luyster FS, Strollo PJ Jr, Zee PC, Walsh JK; Boards of Directors of the American Academy of Sleep Medicine and the Sleep Research Society. Sleep: a health imperative. *Sleep*. 2012;35(6):727-734. Published 2012 Jun 1. doi:10.5665/sleep.1846

115. Kothari DJ, Davis MC, Yeung EW, Tennen HA. Positive affect and pain: mediators of the within-day relation linking sleep quality to activity interference in fibromyalgia. *Pain*. 2015;156(3):540-546. doi:10.1097/01.j.pain.0000460324.18138.0a

116. https://www.britishpainsociety.org/static/uploads/resources/files/pmp2013_main_FINAL_v6.pdf

117. O'Brien EM, Waxenberg LB, Atchison JW, et al. Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *Clin J Pain*. 2011;27(5):425-433. doi:10.1097/AJP.0b013e318208c8e4

Table 1. Micro longitudinal and longitudinal studies investigating the sleep-pain relationship.

Study	Participants	Design	Assessments	Pain → Sleep	Sleep → Pain
Agmon 2014	General population N = 3,421	Baseline; 3.7 year follow-up	Self-report insomnia and back pain onset	No	Yes*
Aili 2018	General population N = 1,249	Baseline; 5-year follow-up; 18-year follow-up	Self-report sleep problems and chronic widespread pain onset	N/A	Yes* (stronger for 5-year follow-up versus 18-year follow-up)
Bigatti 2008	Fibromyalgia N = 492	Baseline; 1-year follow-up	Self-report sleep quality and pain	No	Yes*
Boardman 2006	General population N = 1,589	Baseline, 1-year follow-up	Self-report sleep problems and headache onset	N/A	Yes
Dzierzerski 2010	Insomnia N = 50	Daily for 14 days	Actigraphy; self-report sleep diary and pain	N/A	Yes*
Edwards 2008	General population N = 971	Daily for 8 days	Self-report sleep and pain onset	Yes (weaker)**	Yes***
Generaal 2017	General population N = 1,860	Baseline, 6-year follow-up	Self-report insomnia and chronic multisite musculoskeletal pain onset	N/A	Yes***
Gupta 2007	General population N = 3,171	Baseline; 15-month follow-up	Self-report sleep problems and chronic widespread pain onset	N/A	Yes
Jansson 2012	General population N = 1,746	Baseline; 1-year follow-up	Self-report insomnia and pain persistence	Yes**	Yes**
Jones 2009	General population N = 1,881	Baseline; 4-year follow-up	Self-report sleep problems and musculoskeletal pain onset	N/A	Yes (good quality sleep was predictive of good musculoskeletal health)
Koffel 2016	Chronic musculoskeletal pain N = 250	Baseline; 1-year follow-up	Self-report insomnia and pain severity	Yes* (weaker)	Yes***

Lin 2017	Insomnia N = 1,579	Baseline; 10-year follow-up	Clinician-diagnosed myofascial pain syndrome	N/A	Yes***
Mork 2012	Women N = 12,350	Baseline; 10-year follow-up	Self-report sleep problems and fibromyalgia onset	N/A	Yes***
Nitter 2012	Women N = 1,338	Baseline; 17-year follow-up	Self-report sleep problems and chronic pain onset	N/A	Yes (disrupted sleep was a risk factor for chronic pain onset)
O'Brien 2011	Women N = 22	Daily for 14 days	Actigraphy; self-report sleep diary and daytime pain ratings	Yes***	Yes***
Odegard 2013	General population N = 19,271	Baseline; 11-year follow-up	Self-report insomnia and headache and chronic musculoskeletal complaints	Yes (stronger for headache pain versus chronic musculoskeletal pain)	N/A
Pan 2020	General population N = 1,099	Baseline; 10.7-year follow-up	Self-report sleep and pain; knee radiography	Yes (stronger for knee pain versus multisite pain)	Yes (stronger for multisite pain versus knee pain)
Quartana 2010	Temporomandibular joint disorder N = 53	Baseline; 3-month follow-up	Self-report insomnia and pain	No	Yes*
Salwen 2017	Knee osteoarthritis and insomnia N = 74	Baseline; 6-month follow-up	Actigraphy; self-report sleep diary and CBT-I-related reductions in pain	N/A	Yes* (sleep duration was predictive of pain reduction during CBT-I)
Skarpsno 2021	General population N = 6,033	Baseline; 10-year follow-up;	Self-report sleep quality and chronic pain onset	N/A	Yes (change from good to poor sleep between

		20-year follow-up			baseline and 10-year follow-up was predictive of chronic pain onset at 20-year follow-up)
Smith 2008	Insomnia and major burn injury N = 333	Baseline; 24-month follow up	Self-report insomnia and pain	Yes**	Yes**
Tang 2012	Chronic pain and insomnia N = 119	Daily for 7 days	Actigraphy; self-report sleep and pain	No	Yes*** (sleep quality was predictive of pain the next day)
Tang 2015	General population N = 6,676	Baseline; 3-year follow-up	Self-report insomnia onset and musculoskeletal pain based on American College of Rheumatology criteria	Yes (stronger for widespread pain versus some pain)	N/A
Uhlig 2018	General population N = 13,429	Baseline; 11-year follow-up	Self-report insomnia and chronic musculoskeletal complaints	No	Yes
Vitiello 2013	Osteoarthritis and insomnia N = 367	Baseline; 18-month follow-up	Self-report insomnia and pain severity	No	Yes***
Wiklund 2020	Localized pain N = 959	Baseline; 24-month follow-up	Self-report insomnia and spreading of pain	N/A	Yes

Notes. *p<0.05, **p<0.01, ***p<0.001