

Sleep and Pain: A Biopsychosocial Perspective

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Received: August 06, 2018; **Published:** August 28, 2018

Abstract

This review examines the research of the biopsychosocial influences of sleep and pain. Chronic pain sufferers in general, experience a reduction in sleep quantity and quality (Q/Q). Sleep and pain have a bidirectional relationship, meaning individuals with more severe pain experience worse sleep Q/Q. Disrupted sleep and pain have a cyclic relation with negative physical and mental states. Hyperalgesia is common among those suffer from pain and/or sleep disturbances, and can be due to inflammation and/or sterile inflammation responses from pain and disrupted sleep. This can put the body in a catabolic state, causing bone differentiation and a decrease in tissue repair. Medications for pain and symptoms associated with pain, have been demonstrated to disrupt the restorative functions of sleep, interrupt normal neurochemistry processes of the brain during sleep, and prevent rapid-eye movement during sleep. Individuals suffering from sleep disturbances and pain experience a myriad of negative mental states due to pain and reduced quality of sleep, which can include depression, anxiety, and substance abuse issues. A biopsychosocial approach is crucial when treating individuals with pain issues, as many medications will hinder their ability to recover from disruption of sleep, whereas improvement in physical and psychosocial health appear to improve sleep.

Keywords: Sleep; Pain; Hyperalgesia

Introduction

A substantial amount of individuals that experience poor sleep also commonly report undergoing chronic pain [1]. Findings also suggest that individuals that live with chronic pain and disrupted sleep are more likely to display poor mental health, decreased social functioning, fatigue, and less involvement with cherished activities [2]. More recent studies concerning the relationship between pain and sleep hygiene have begun focusing on attention and mood as other facilitating features [1]. The dynamic between pain and sleep were previously thought to share a bidirectional relationship, commonly seen as pain disrupting sleep, and poor sleep exaggerating the intensity of pain [1]. Pain is often seen as being a predictor of sleep quality, while quality of sleep mediates the association between pain and fatigue [2]. Individuals experiencing pain concurrently with sleep disturbances might possess greater pain severity and allocate more of their attention on the pain they are feeling. Consequently, this amplified focus on pain is often prophetic of increased sleep disturbance [1]. Disrupted sleep may jeopardize the reparative functions sleep provides, therefore prolonging the healing process and increasing an individual's sensitivity to pain [1].

Pain presents a myriad of issues for the patient and provider which can include agitation, decreased life span, and increased risk of substance abuse [3,4]. A rapidly growing body of research is exploring the bidirectional nature of pain and sleep. In this model, pain, through a variety of mechanisms, decreases the quality and duration of sleep. Decreased sleep quality and duration then, in turn, increases sen-

sitivity to pain through a variety of mechanisms [5,6]. This effect is significant to the degree of researchers being able to predict elevated pain levels based on sleep complaints the night prior [6-10]. Increased understanding of the relationship of pain and sleep presents many possible advances in the realms of sleep and pain management.

Sleep, Pain, Stress and Inflammation

Sleep has a multitude of restorative functions for the body, accelerating the repair and/or development of virtually every tissue and humor [9,10]. As to pain specifically, a reduction in quality and/or quantity (Q/Q) of sleep can result in a global increase in inflammatory cytokines including: tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), C-reactive protein (CRP), and other inflammatory markers [11-15]. TNF-alpha promotes osteoclast differentiation (degrading of the bone matrix) and survival, potentially compounding with other pain sources or enhancing existing musculoskeletal pain via further degradation of skeletal tissue [16,17]. IL-6 is a potent inflammatory cytokine, essential for regulating immune responses, but potentially damaging when chronically held at high concentrations [18-21]. CRP is a strong indicator of an inflammation, and is produced by the liver and released when the body detects elevated IL-6 and T cell activation. The role of CRP is to reduce lysis of downstream cell membranes [12-15,22,23]. Elevated IL-6 and CRP has been detected in individuals that suffer from obstructive sleep apnea [24]. Disrupted sleep due to pain, apnea, or other illnesses may indeed be partially responsible for a phenomenon known as "sterile inflammation", an inflammatory response not explicitly due to an infection [25-28].

These inflammatory cytokines, and many others, bind to nociceptors within the peripheral nervous system (PNS). In acute pain, such as a scrape, this effect is regional and temporary. In sleep Q/Q reduction-related inflammation, the response is global and chronic [20,26,29]. This results in pain virtually every area with a PNS nociceptors. This enhancement, or hyperactivity, of nociceptors increases the release of neurologically active pain chemicals including Substance P and Glutamate, Brain-Derived Neurotrophic Factor [BDNF], amongst others [30-33]. Hyperalgesia (over sensitization) can result, lowering the threshold for painful stimuli, even in completely "normal" tissues [5,6,8,31-33].

Stress is a global response to a stressor enveloping essentially all systems and organs. An early evolutionary tool, modern humans experience stress from non-life-threatening events such as job loss or relationships. Pain initiates and maintains a global stress response which is, for the most part, a negative feedback response. Prolonged pain can begin to disrupt the negative feedback response, leaving the body in a prolonged, global state of stress [34-36]. Worry or anxiety over the pain itself is a common phenomenon in prolonged pain patients, and can create additional stress independent of stress from the "real" pain [1,6,37]. A slew of hormones are responsible for global stress response, but one hormone in particular is cortisol [35,38]. This stressed state results in an increase in serum energy abilities (glucose, glucagon, fatty acids, free ATP), increased blood pressure, increased blood/brain oxygen, and overall increased alertness [39,40].

Reduction in sleep Q/Q has a relation with inflammatory cytokines. These chemicals signal pain by activating PNS nociceptors and creating pain through tissue damage. This results in global pain, hyperalgesia, and potential worry/anxiety. Neuroendocrine responses to pain create a stress response, resulting in an increased state of alertness. This mental state makes falling and staying in sleep more difficult, reducing sleep Q/Q [1,5,7-11,13-15,17,23,30,40,41]. In terms of sleep, stress (such as from pain and anxiety) is quite maladaptive. Sleep involves a decrease in serum energy abilities, decreased blood pressure, normal blood/brain oxygen, and a lack of conscious alertness. Patients suffering from insomnia tend to have heightened measurements of the above criteria [40,41]. Studies have demonstrated clinically-diagnosed insomniacs chronically experience reduced sleep Q/Q, abnormal and/or irregular sleep wake cycles, amongst many other comorbidities such as pain [42,43]. A study by Savard and Morin [44] found 30-50% of patients experiencing chronic pain conditions (e.g. fibromyalgia, rheumatoid arthritis, osteoarthritis, and musculoskeletal pain) also had reported suffering from insomnia. Pain has also been associated with reduced sleep time and suicidal ideation, similar to symptoms of major depressive disorder [45].

Since pain negatively impacts sleep Q/Q, an obvious improvement should be the removal (or, more realistically, reduction) of day and nighttime pain [6,9]. This does not occur without its complications. Many pain drugs negatively influence sleep Q/Q independently. It is worth noting that studies evaluating the effects of pain drugs on sleep almost assuredly have one of two flaws: the inability to isolate the sleep effect from the underlying pain-causing ailment or the participants are healthy young volunteers that would not benefit from the reduction in pain [46,47].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs relieve pain by inhibiting cyclooxygenase [COX-1 (common) or COX-2 (rare)], reducing prostaglandin [48-50]. PGs, particularly PG-D2 and PG-E2 are involved in the sleep and wake response, respectively. Short-term NSAID usage in healthy, young individuals resulted in poorer sleep efficiency and more nocturnal awakenings [51-53]. The Murphy and colleagues [51] study also evaluated the effect of NSAIDs on body temperature and salivary melatonin. When taken at night before sleep, NSAIDs hindered the body's ability to decrease body temperature and produce melatonin [54]. Importantly to sleep's restorative properties and the sleep-pain cycle, melatonin is an anti-inflammatory and anti-oxidative agent [55,56].

Steroidal Anti-Inflammatory Drugs (SAIDs)

The mechanisms of how SAIDs (corticosteroids) reduce inflammation are numerous and complex. In short, SAIDs reduce inflammation by suppressing the immune system's inflammatory response and through general immunosuppression [57,58]. SAIDs can disrupt typical sleep Q/Q by disrupting homeostasis of brain mineralocorticoid and glucocorticoid, resulting in a stimulatory effect [59,60]. The effect appears to be dose dependent, with more sleep Q/Q reduction as dosing increases [61]. Fortunately, most SAIDs have relatively short half-lives, and a single morning dose can reduce sleep Q/Q in most adults [62,63]. More severely, SAIDs can induce a rare disorder known as steroid psychosis (SP), an extreme and potentially chronic disruption of normal behaviors and cognitive functions. SP can be present during treatment or during weaning/withdrawal phase of coming off SAIDs. Symptoms include insomnia, anxiety and even clinical psychosis in rare occasions [57,64-66].

Paracetamol (APAP)

There is currently little research on the effect of paracetamol (also known as acetaminophen or APAP) on sleep. A study of 210 osteoarthritis patients found that patients report better sleep with extended release APAP over standard APAP at a 2:1 ratio [67]. Another study evaluated an off-label self-prescribed use of APAP as a sleep aid in older adults, and found no significant improvement in sleep Q/Q from sleep diaries [68].

Opioids and Substance Abuse

Disrupted sleep is also common among patients of substance use including alcohol, nicotine, marijuana, and heroin [69]. Sleep disturbances often acts as a salient trigger for relapse, and a reliable predictor of treatment outcome. Unfortunately, sleep related issues found among substance use patients have been seen to persist for weeks, months, or even years, upon termination of substance use. More importantly, individuals will often use alcohol to self-medicate symptoms of insomnia resulting in considerably higher rates of relapse [69].

When treating chronic pain, both pharmacological and psychological interventions should be utilized to enhance physical and cognitive restoration [1]. Regrettably, certain pain relieving compounds have been found to cause sleep fragmentation, and often times promote symptoms of insomnia [1]. The use of prescription opioids (PO) are commonly found among individuals experiencing chronic pain; although it is not uncommon for individuals to report using PO for alternative reasons, for example to improve sleep [68]. Opioids notably have a wide range of side effects on sleep, pain, immunology, and essentially every other system. Many of these side effects are antagonistic. For example, opioids relieve pain and have sedative effects, but can also cause hyperalgesia and decrease sleep Q/Q [6,8,70]. Opioids have been demonstrated to interfere with many aspects of sleep including sleep respiration (potentially fatal), duration, sleep pattern transition, and waking fatigue [6,71-74]. Hartwell and colleagues [68] concluded roughly 80% of PO dependent individuals also report experiencing greater pain severity, pain interference, and numerous sleep disturbances including: total sleep time, sleep efficiency, delayed onset of sleep, and total time awake.

Depression, Anxiety and Antidepressants

Insomnia is often interwoven with the future development of psychopathology, specifically depression and anxiety, as well as substance abuse and suicide ideation/intention [75,76]. Research indicates that symptoms of insomnia often precede depressive symptoms, therefore identifying insomnia as not only a symptom of depression, but also a potential predictor of depressive symptoms [76,77]. Depression is often co-occurring with pain and fatigue and has been associated with a decline in physical activity, self-efficacy, and function ability [2]. Greater pain interference in the presences of daily events likely intensifies fatigue, anxiety, and sleep disruption, all of which increase the prospect of depressive symptoms [2]. A decline in daytime activities might lead individuals to alienate themselves from others, this isolation might induce dysfunctional ruminative cognitions concerning their pain and uncontrollability of sleep, resulting in feelings of helplessness and hopelessness [1,78].

It is believed that insomnia is maintained through negative cognitive activity, including rumination and dysfunctional beliefs in terms of sleep [79]. On the other hand, anxiety is comprised of two components: worrying (cognitive component) and somatic anxious arousal (physiological component; [79]). These dysfunctional thoughts are often found at the root of how poor sleep influences daytime functioning and wellbeing [79]. Symptoms of anxiety often work in parallel with depressive symptoms, with negative cognitive activity being abundant within both mood disorders. The relation between sleep disturbances, mood disorders, and negative cognitive activity often perpetuate symptoms of insomnia [79,80]. Similarly, social anxiety has been found to be associated with an increase of insomnia symptoms as well as noticeability of a sleep problem to others and distress regarding sleep disturbances [81]. Social anxiety negatively impacts numerous areas of daily life: education, employment, and interpersonal relationships. Compared to healthy sleepers, individuals suffering insomnia are more likely to ruminate over social situations and possible negative outcomes while preparing to fall asleep [82]. Avoiding social engagements due to disrupted sleep and rumination might result in a reduction of involvement in daily activities. This lack of activity throughout the day further maintains nightly sleep difficulties [1,82]. It seems that focusing on correcting catastrophic thoughts might assist better-quality sleep outcomes, resulting in a general reduction in social anxiety [81].

Different types of antidepressants such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) have been used in the treatment of depression, anxiety, and chronic pain. Exactly how these drugs reduce pain is unknown, though two popular theories suggest serotonin and norepinephrine reuptake inhibition and/or sodium channel inhibition as a possible responsible mechanism [83,84]. These drugs severely limit, or even eliminate (in the case of MAOIs), rapid-eye movement (REM) sleep. While this used to be believed as their mechanism of action as an antidepressant, it is now understood that this is a major side effect of antidepressant drugs along with sleep architecture modulation [85-87]. Evidence suggests that severely limiting or eliminating REM sleep, and taking TCAs (except amitriptyline), SSRIs, and MAOIs appear to have little to no cognitive or memory effects does not affect cognitive or memory function [86,88,90]. Individual's measures of sleep quality also do not seem change between placebo or single-dose SSRI [90]. There is also evidence to the contrary, where antidepressants negatively affected objective and subjective sleep quality (which includes nocturnal awakenings), but still no impact on cognitive or memory function [88,91]. The area of antidepressant and its influence on sleep is rapidly evolving and warrants further research [89].

Emotional dysfunction

Growing evidence suggests that sleep deprivation also drastically impacts empathy and emotional functioning of an individual. Sleep loss increases physiological reactivity when confronted with emotional stressors, reduces the ability to cope with stress, and is associated with poor frustration tolerance, as well as a skewed perception of the intentions of others. Furthermore, sleep disturbances are related to a substantial decline in understanding another individual's emotional response, resulting in inadequate interpersonal skills, empathy, stress management capabilities, and increased impulsivity [92]. Sleep deprivation has also been correlated with diminished responsiveness to faces displaying fear and sadness [93]. With this said, being able to properly process emotional stimuli is crucial to empathizing with another individual's emotions, feelings, and thoughts, all of which are obligatory skills in sustaining strong social connections [93]. Sleep quality in general has been cited as a predictor of empathic abilities, regardless of the intensity of the stimuli being presented [93].

Conclusion

Therefore, when considering the treatment of chronic pain including intervention options that encompass the co-occurring factors and using the biopsychosocial approach would be beneficial in reducing the reliance upon pharmacological treatments that actually impede sleep Q/Q [1]. Cognitive behavioral therapy (CBT) has been effective in relieving sleep disturbances, thus alleviating pain-associated disability, and enhancing mood [1]. For example, improving the quality of sleep could indirectly improve the severity of pain among patients while lessening an individual's depressive symptoms and cognitive disturbances [1]. Other findings suggest that relaxation and guided imagery interventions actively improve fatigue and sleep disturbances among individuals with chronic pain [94]. Bruck and colleagues [95] found unrealistic beliefs regarding sleep as commonplace, with healthy sleep being mistakenly seen as unbroken throughout the night. Simply educating individuals about healthy sleep might show preventative health implications and reduce sleep anxieties. Lastly, research suggests that staying active, engaging in physical exercise, and living a satisfying social life functions as protective factors against insomnia symptoms and other sleep related disturbances, and should be recommended in patients undergoing treatment for sleep disturbances [81,96,97].

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Volume 4 Issue 9 September 2018

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