

# Insomnia ROUNDS

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## Pain, Analgesia, and Insomnia: Stopping the Cycle

By Florian Chouchou, PhD, and Gilles J. Lavigne, DMD, MSc, PhD

Poor sleep and pain form a vicious cycle: sleep deprivation can alter pain processing and cause hypersensitivity, and pain in turn typically reduces sleep duration, continuity, and architecture. Opioids, which are commonly prescribed for both acute pain (eg, during the postoperative period) and for chronic pain conditions, have also been shown to disturb the depth and continuity of sleep, both on their own and in interaction with pain. This issue of *Insomnia Rounds* addresses the possible role of pain in sleep disruptions among patients suffering from insomnia. It also reviews evidence for the alteration of pain processing in insomnia, with a particular emphasis on the potential role of pain in sleep disruptions and the subsequent alterations in pain processing in different patient populations. The potential physiological mechanisms associated with opioid use and how certain psychological and emotional factors may contribute to disruptions in sleep quality and pain relief are also discussed.

Insomnia is defined as “difficulty initiating or maintaining sleep, as well as nonrestorative sleep with decreased daytime functioning that persists for at least four weeks.”<sup>1</sup> Insomnia is one of the most commonly encountered sleep disorders in medical practice, affecting about 10% of the population in western industrialized countries. The prevalence is higher among older adults and women.<sup>2,3</sup>

Insomnia may be a symptom secondary to one (or more) of a number of psychiatric or medical disorders, or it may be the result of environmental disturbances or stressful situations. As a manifestation of stress or as a stressor itself, insomnia would be expected to promote a state of hyperarousal. From this perspective, pain may be considered equivalent to insomnia as an activator of the stress system, activating both the hypothalamic-pituitary-adrenal (HPA) axis of the stress system and the sympathetic system.<sup>4</sup> Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with present or potential tissue damage, or described in terms of such damage.”<sup>5</sup>

The prevalence of chronic pain ranges from 15%–19% in the Canadian population,<sup>6</sup> and chronic painful conditions are frequently associated with sleep complaints. Between 30% and 88% of chronic pain patients report poor sleep and/or a feeling of being unrefreshed upon awakening.<sup>7</sup> In turn, patients suffering from insomnia frequently report daily pain,<sup>8</sup> and several cross-sectional and longitudinal studies have reported a correlation between insufficient or disturbed sleep and pain complaints.<sup>9</sup>

In the general population, recent epidemiologic data reveal a relationship between sleep duration and the frequency of next-day pain. Transitioning from a night of relatively normal sleep duration to a night of <6 hours or >9 hours of sleep was related to substantial increases in how frequently pain was experienced the next day.<sup>10</sup>



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**Table 1: Studies on the effects of pain stimulations on sleep in healthy subjects**

Study	Sleep intervention	Main results
Lavigne et al <sup>17</sup>	Thermal stimulation	Pain stimulations induce arousal during sleep
Lavigne et al <sup>18</sup>	Thermal stimulation	Pain stimulations induce heart rate increase in all sleep stages
Lavigne et al <sup>16</sup>	Intramuscular infusions	Pain stimulations induce cortical arousals in all sleep stages
Bastuji et al <sup>15</sup>	Laser stimulation	Brain-evoked potentials to pain are preserved in all sleep stages
Chouchou et al <sup>4</sup>	Laser stimulation	Sympathetic cardiac reactivity is related to cortical arousal

## Pain and Opioid Use as Disruptors of Sleep

### *Do people with chronic pain experience sleep disruption?*

Chronic painful conditions are frequently associated with sleep disturbances, including the following:<sup>11</sup>

- shorter sleep duration
- changes in sleep continuity and sleep architecture
- increased daytime sleepiness

People suffering with painful conditions report low levels of sleep efficiency, similar to that in the insomniac population. similar to that in the insomniac population. They also perceive their depth of sleep to be decreased; this complaint has been confirmed by studies showing that they have low  $\delta$  electroencephalographic (EEG) power.<sup>12,13,14</sup> However, this finding does not necessarily imply a direct effect of pain on sleep. Experimental studies of painful stimuli during sleep in healthy subjects are important to better understand the effect of pain on sleep.

### *Does experimental pain disturb sleep in healthy subjects?*

Nociceptive experimental stimulations have been applied during sleep to challenge pain perception. These painful stimuli are able to induce cortical arousals during all stages of sleep (Table 1).<sup>15–18</sup> Central nervous system (CNS) reactivity to nociceptive stimuli delivered during sleep also induces a concomitant sympathetic reactivity that changes cardiac and respiratory parameters under autonomic control.<sup>4</sup> These studies suggest that painful stimuli delivered during sleep – independently of other environmental factors or physiological co-factors – are able to induce a response in the CNS that is similar to the alterations in sleep patterns present in patients complaining of sleep altered by pain.

### *What effects do opioids have on sleep?*

Opioids (eg, codeine, morphine, hydromorphone, oxycodone, and fentanyl) are first-line agents used to treat a variety of pain conditions.<sup>19,20</sup> They are known to have significant effects on sleep.<sup>21,22,23,24</sup> Therefore, the use of opioids

to manage pain is a further putative factor that may cause sleep disturbance. Opioids may also disrupt breathing and, as a result, they constitute a major concern in patients with sleep apnea.<sup>21,23</sup> With acute administration to healthy, pain-free volunteers, opioids reduced both rapid eye movement (REM) and slow-wave (non-REM stages 3–4) sleep duration and promoted wakefulness. Therefore, sleep and awake states may be disturbed by both pain and by clinical pain management with opioids. In patients at risk for sleep disturbance, alternatives should be considered, such as non-steroidal anti-inflammatory drugs (NSAIDs), which appear to have a less deleterious influence on sleep.<sup>11</sup>

## Sleep Disruption as a Catalyst of Pain

### *Do people with insomnia experience pain more than good sleepers?*

People with insomnia often report spontaneous pain. Haack et al<sup>8</sup> compared the effects of laboratory pain testing on 17 individuals with primary insomnia (mean 22.6 years) and 17 health controls over 2 weeks. This study assessed the inhibition of the perception of primary experimental pain using concurrent stimulation of endogenous pain pathways. The primary insomnia group reported pain symptoms on twice as many days as their healthy counterparts ( $9.4 \pm 1.0$  days versus  $4.8 \pm 1.1$  days;  $P < 0.05$ ), mainly higher levels of physical discomfort and generalized body pain rather than pain at specific body sites. Those in the insomnia group demonstrated decreased pain thresholds compared to healthy volunteers in experiments using thermal and mechanical pain, and they reported that their pain was more intense ( $20 \pm 16$  versus  $12 \pm 7$  units, averaged from the daily patient-reported scores on a 0–100 mm visual analogue scale). These results point to an overall dysfunctional pain inhibition system, and provided evidence that the central modulation of pain may be altered in people with insomnia. The authors noted that, while pain intensity ratings (temporal summation) further to heat pulses increased gradually as expected in the control group, they declined markedly after initial increase to final scores below baseline levels in insomnia patients. Therefore, insomniacs

**Table 2: Main studies on the effects of sleep disruptions on pain in healthy subjects**

Study	Sleep intervention	Nights	Main results
Kundermann et al <sup>28</sup>	Total sleep deprivation	2	Decreased heat pain threshold
Haack and Mullington <sup>29</sup>	Partial sleep deprivation	10	Increased reported pain-related discomfort
Haack et al <sup>30</sup>	Partial sleep deprivation	12	Increased reported pain-related discomfort
Smith et al <sup>27</sup>	Forced awake, partial and total sleep deprivation	3	Increased reported pain-related discomfort and decreased pain-inhibition function
Haack et al <sup>30</sup>	Total sleep deprivation	3	Increased reported pain-related discomfort
Tiede et al <sup>34</sup>	Partial sleep deprivation	1	Increased reported pain response to heat stimulation
Azevedo et al <sup>32</sup>	Total sleep deprivation	2	Increased reported pain response to heat stimulation
Irwin et al <sup>41</sup>	Partial sleep deprivation	1	Increased reported daily pain-related discomfort
Schuh-Hofer et al <sup>35</sup>	Partial sleep deprivation	1	Decrease in mechanical, heat, and cold pain threshold

may be particularly vulnerable in pain-inducing situations such as during surgery and postoperatively. Indeed, of several factors known to affect postoperative pain, chronic sleep complaints before surgery constituted the strongest determinant; the risk was 4 times higher than in those without sleep complaints).<sup>25</sup>

In a wide cross-sectional study of the epidemiology, classification, and effects of insomnia involving 25 579 individuals from Europe (including France, the United Kingdom, Germany, Italy, Portugal, Spain, and Finland), Ohayon and Reynolds<sup>26</sup> concluded that pain due to musculoskeletal or articular diseases (ie, arthritis, backache, limb pain) was the organic disease most frequently associated with insomnia. In their study, 14.6% of subjects who met insomnia criteria suffered from painful disease as compared to 3.4% subjects without insomnia (odds ratio [OR] 4.9; 95% confidence interval [CI] 4.3 to 5.7). The second most commonly associated disease was heart diseases, which was found in 5.4% of insomnia subjects (OR 2.1; 95% CI 1.7 to 2.6).

#### *Does sleep disruption in healthy individuals influence pain perception?*

Studies of the impact of sleep disruption on pain perception in healthy subjects<sup>27,28</sup> have demonstrated that total and partial sleep deprivation induced pain-related discomfort such as stiffness, joint pain, back pain, and headache, whereas recovery nights were associated with decreased discomfort (Table 2).<sup>27-35</sup> Forced awakening also increased the capacity to cause pain and induce the dysfunctional pain inhibition system compared to simple sleep restriction.<sup>27</sup> Sensitivity has been the most frequently tested indicator, and mechanical and heat pain thresholds appear to decrease after sleep deprivation. More recently, 2 studies using heat laser stimulation in healthy subjects revealed that stimulation at the same intensity was perceived as

more intense after partial or total sleep deprivation.<sup>32,34</sup> A recent study showed that total sleep deprivation resulted in a generalized decrease in the mechanical, cold, and heat pain thresholds,<sup>35</sup> suggesting that sleep deprivation induces hyperalgesia.

#### *Does sleep disruption exacerbate pain perception in patients with clinical disorders?*

Chronic painful conditions are frequently associated with sleep disturbances, while worsening pain is often followed by a night of poorer sleep.<sup>36</sup> For many individuals, sleep quality is considered to be an important predictor of pain the next day.<sup>37</sup> This vicious cycle has also been reported by patients experiencing chronic pain due to conditions such as fibromyalgia<sup>36</sup> or severe skin burns,<sup>38</sup> although it has not been reported for all chronic pain conditions.<sup>39</sup> There are also wide interindividual differences.

The relationship between sleep disruptions and the pain process has been tested in different populations, including patients with major depression,<sup>40</sup> rheumatoid arthritis,<sup>41</sup> somatoform pain,<sup>42</sup> and gastroesophageal reflux<sup>43</sup> (Table 3). Overall, most of the results indicate that sleep disruption, specific sleep stage deprivations, or sleep continuity disturbances altered pain perception and caused pain. These results demonstrate that total and partial sleep deprivation induced pain-related discomfort such as stiffness, joint pain, back pain, and headache, whereas recovery nights were associated with a decreased intensity of discomfort in patients with major depression, rheumatoid arthritis, and somatoform pain.<sup>40-44</sup>

In addition, the effect of sleep deprivation on pain in patients is greater than in healthy subjects.<sup>43</sup> Some patients may be more vulnerable to the effects of insufficient or disrupted sleep and, in some situations, sleep disturbances should be considered as a risk factor for those vulnerable patients who could go on to develop persistent pain.

**Table 3: Studies on the effects of sleep disruption on pain in different patient populations**

Study	Population	Sleep intervention	Main results
Schey et al <sup>43</sup>	Patients with gastroesophageal reflux	Partial sleep deprivation	Increased reactivity to pain and intensity rating
Kundermann et al <sup>40</sup>	Patients with major depressive symptoms	Total sleep deprivation	Decreased reporting of cold and heat pain threshold
Irwin et al <sup>41</sup>	Patients with rheumatoid arthritis	Partial sleep deprivation	Increased reporting of daily pain-related discomfort
Busch et al <sup>42</sup>	Patients with chronic somatoform pain	Total sleep deprivation	Increased reporting of daily pain-related discomfort

Anxiety, pain catastrophizing (ie, an exaggerated negative mental state during an actual or anticipated painful experience), or depression could render these patients more vulnerable to pain.

#### *Do psychological factors play a role in the interaction between sleep and pain in insomnia?*

A possible explanation for altered pain control caused by sleep disruption and insomnia could be attention and emotion dysfunctions as they are important modulators of the pain experience.<sup>34,45,46</sup> Tiede and colleagues<sup>34</sup> demonstrated that sleep disruptions were associated with a significantly weaker ability to disengage oneself from painful stimulation. Moreover, pain is a sensory and emotional experience that triggers physiological and psychological reactions. Pain is influenced by anxiety, pain catastrophizing, and emotional state, especially negative emotion. Sleep loss and insomnia not only enhance pain but also alter emotional well-being,<sup>29</sup> an integral part of the pain experience. Sleep disruption in particular is known to promote negative emotions and anxiety, suggesting that it can amplify pain indirectly.<sup>47,48</sup> Depression is frequently present in patients with insomnia<sup>49</sup> and may also be a mediator of the association between sleep and pain. In chronic pain patients, those with depression and insomnia reported greater levels of emotional distress and more severe pain.<sup>50</sup>

Taken together, these studies emphasize that depression, anxiety, and emotional dysregulation may be potential mediators that contribute to the interaction between sleep disturbance and pain modulation. In insomnia patients, these psychological cofactors of the relationship between sleep and pain are especially relevant, because it is well known that insomnia alters cognitive and emotional functions.<sup>46</sup>

## Conclusion

Clinical, experimental, and epidemiological data point to a relationship between insufficient or disturbed sleep and pain perception. In insomnia, pain may contribute to the hyperarousal state and sleep disturbances, whereas insufficient or disturbed sleep may in turn contribute to pain complaints, altering the central modulation of pain. Moreover, psychological factors in some insomniacs – such as depression, anxiety, and emotional dysregulation – may play a role in the relationship between sleep and pain. It is important to remember that the complaint of pain in patients with insomnia is closely linked to disturbed sleep, since they are particularly vulnerable to pain. Thus, the management of pain and insomnia includes improvements in life hygiene, cognitive and behavioral treatment, and medication to improve both pain and sleep – or pain or sleep – depending on each individual case.<sup>47</sup>

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## UPCOMING CONFERENCES

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