

# The Bidirectional Relationship Between Perioperative Sleep Deprivation and Postoperative Pain — Mechanisms and Clinical Implications: A Narrative Review

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**Abstract:** Although the understanding of pain mechanism and management has made substantial progress, postoperative pain relief is still an important health care problem. Surgical patients also often report preoperative and postoperative sleep problems. Clinical and experimental studies show that chronic pain and sleep disorders influence each other. Pain disturbs sleep, and sleep deprivation or sleep disorders increase pain. However, there are still many problems about the direction of causality between them and the mechanism that may explain their relationship. In-depth subjective and objective evaluation of pain and sleep supports the view that sleep disorder is a more powerful and reliable predictor of pain, and pain is a predictor of sleep disorder. Recent progress in multimodal imaging, molecular biology, and neural circuit analysis has uncovered how sleep deprivation — especially in the perioperative setting — influences pain sensitivity, the transition to chronic pain, and brain function through mechanisms spanning peripheral nerves, the spinal cord, subcortical areas, and cortical structures.

**Keywords:** postoperative pain, sleep disturbance, sleep deprivation, mechanisms

## Introduction

Chronic pain is a major global health burden, affecting approximately 20–30% of the adult population worldwide, with significant implications for quality of life, mental health, and socioeconomic costs. According to the Global Burden of Disease Study, chronic pain conditions—such as low back pain, headache disorders, and osteoarthritis—are among the leading causes of years lived with disability.<sup>1</sup> In the perioperative context, inadequate pain management remains a persistent challenge, contributing to delayed recovery, increased opioid use, and the transition from acute to chronic postoperative pain.<sup>2</sup>

Accumulating evidence has revealed a robust and bidirectional relationship between sleep and pain. Epidemiological studies estimate that individuals with chronic pain are two to three times more likely to experience sleep disturbances than those without pain, while poor sleep quality—particularly insomnia and short sleep duration—has been shown to predict the onset and exacerbation of pain.<sup>3</sup> Meta-analyses suggest that sleep problems increase the risk of developing chronic pain by approximately 30–50%, and that improvements in sleep are associated with clinically meaningful reductions in pain intensity.<sup>4</sup> Despite this well-established association, the mechanistic pathways linking sleep disruption and pain remain incompletely understood, particularly in the postoperative setting.

Although several reviews have addressed the general relationship between sleep and pain, most have focused on chronic pain populations or experimental sleep deprivation in healthy volunteers. Few have systematically synthesized

the bidirectional interplay between postoperative sleep disturbance (PSD) and postoperative pain, especially in light of recent advances in neuroimaging, molecular biology, and neural circuit research. Moreover, the perioperative period offers a unique window to study the dynamic interaction between sleep and pain under controlled surgical and anesthetic conditions.<sup>3</sup> Given the increasing recognition of PSD as a modifiable risk factor for poor surgical outcomes, there is a pressing need to update and integrate current knowledge to inform clinical practice and guide future research.

This narrative review aims to: (1) summarize the clinical evidence supporting the bidirectional relationship between postoperative sleep disturbance and pain; (2) synthesize findings from experimental sleep deprivation studies that elucidate causal mechanisms; and (3) explore the underlying neurobiological mechanisms—from peripheral and spinal pathways to brain circuits and molecular signaling—that link sleep disruption and pain processing. By integrating clinical and mechanistic perspectives, this review seeks to provide a comprehensive framework for understanding sleep–pain interactions in the perioperative setting and to identify potential targets for therapeutic intervention.

## Methods

We here conducted a literature search of the electronic databases of PubMed, Embase, Web of Science, and Cochrane Library between January 1990 and December 2025, the search terms used including combinations of “postoperative pain”, “sleep disturbance”, “sleep deprivation” and “mechanisms”. Only peer-reviewed original articles published in English were included in the study. The study selection process for the narrative review is shown in [Figure 1](#). A systematic literature search identified 406 potentially relevant studies. After eliminating duplicates and excluding all ineligible studies, 33 studies were included. Furthermore, two crucial studies retrieved through manual search were also included. Ultimately, 35 studies were included in the narrative review.

## The Bidirectional Relationship Between Sleep and Pain Experiences

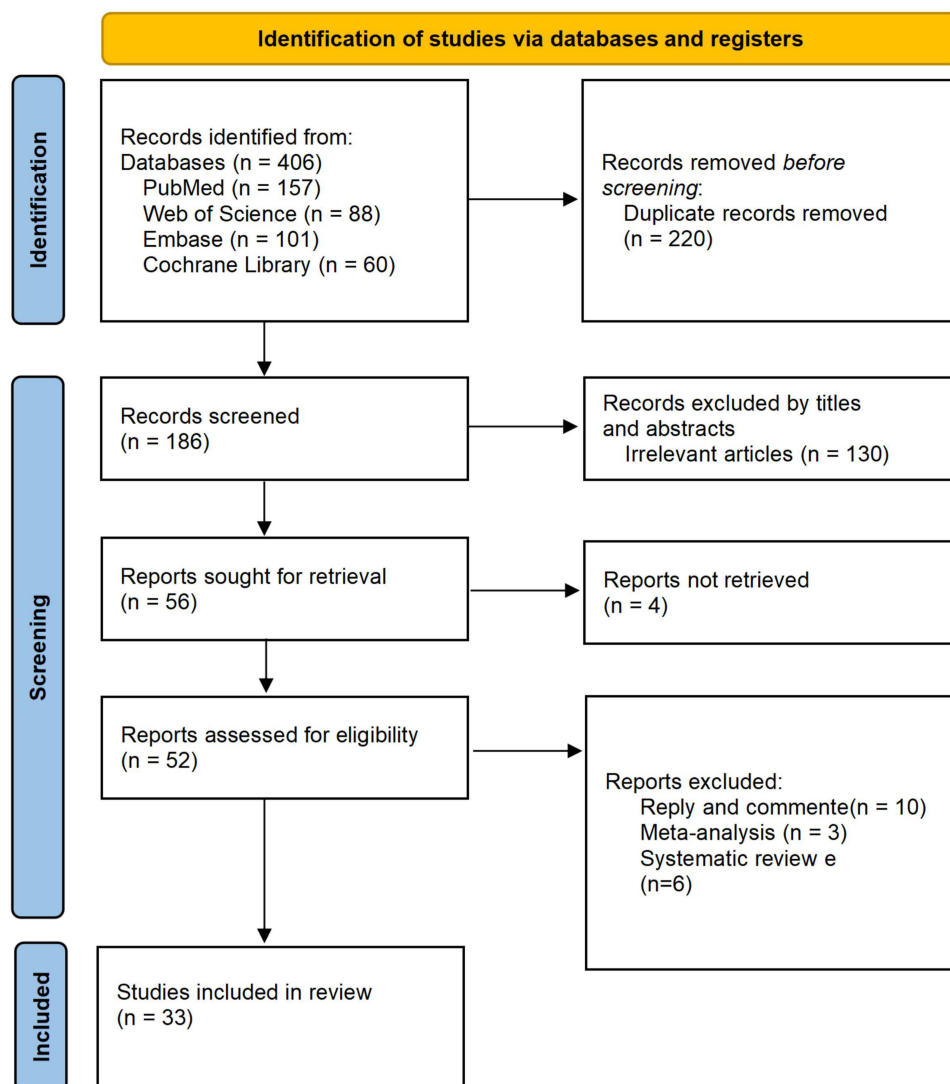
Postoperative pain and sleep disturbances are two of the most common challenges faced by surgical patients during recovery. Extensive clinical observations and studies have shown that these two issues are not isolated but rather form a mutually reinforcing vicious cycle. For details, see [Table 1](#).

### Sleep Disturbances are Prevalent Among Surgical Patients Postoperatively

PSD is a common phenomenon, as evidenced by multiple studies from various perspectives. Stoop et al, in a large Dutch multi-center study, found that 64.1% of surgical patients reported sleep disturbances, establishing PSD as a common perioperative complication. In recent years, research methods have evolved from describing prevalence rates towards exploring patient heterogeneity and underlying mechanisms.<sup>5</sup> Bartosiak et al focused on knee arthroplasty patients, highlighting the complex bidirectional relationships between sleep, pain, and psychosocial factors such as anxiety, and emphasizing the high prevalence of obstructive sleep apnea (OSA).<sup>6</sup> Yang et al identified three PSD severity subgroups (mild, moderate, severe) using Latent Profile Analysis. They quantified key modifiable risk factors: higher body mass index, longer anesthesia duration, greater pain, and higher anxiety increase the risk of moderate-to-severe PSD. This underscores the heterogeneity of PSD and guides personalized care.<sup>7</sup> These studies have all revealed the existence and prevalence of PSD.

### Postoperative Pain is a Key Driver of Sleep Disturbances

After establishing the prevalence of postoperative sleep disturbances, researchers began to explore their underlying causes and consistently identified postoperative pain as a critical driver. Büyükyılmaz et al, in their study of Turkish orthopedic patients, explicitly identified pain as the primary factor affecting postoperative sleep quality (accounting for 45%), and found a significant correlation between nighttime pain intensity and deteriorated sleep quality.<sup>8</sup> Giordano et al provided corroborating evidence from another angle, demonstrating that effective pain management—specifically, peripheral nerve blocks—indirectly improved postoperative sleep quality by alleviating pain.<sup>9</sup> Multimodal analgesic strategies, such as the combined use of dexmedetomidine and regional nerve blocks, can reduce opioid consumption, thereby improving postoperative sleep and cognitive function.<sup>20</sup> This indicates that the level of postoperative pain directly determines the severity of sleep disturbances, and pain control is a crucial pathway to improving sleep. Additionally, Koffel et al, in their analysis of data



**Figure 1** Flowchart of study selection.

from veterans with chronic musculoskeletal pain, supported this directional relationship, showing that changes in pain predicted subsequent changes in sleep complaints.<sup>10</sup>

## Sleep Disturbances, in Turn, Exacerbate Pain Perception and Delay Recovery

As research deepened, it became evident that the relationship between sleep and pain is not unidirectional; sleep disturbances themselves can exacerbate pain perception, forming a vicious cycle. Edwards et al, in a microlongitudinal study of the general population, first revealed a prospective association between sleep duration and next-day pain reports, finding that both sleeping less than 6 hours and more than 9 hours were associated with increased pain frequency the following day. This finding has been repeatedly validated in surgical populations.<sup>11</sup> The study by Cremeans-Smith et al on total knee arthroplasty patients was groundbreaking, as it was the first to confirm that postoperative sleep disruption mediates the relationship between early postoperative pain and later functional limitations.<sup>12</sup> In other words, pain not only directly leads to functional decline but also indirectly affects long-term recovery through the intermediary of disrupted sleep. Azizoddin et al, in a longitudinal study of breast cancer patients, also found that postoperative sleep disturbance was significantly associated with higher pain severity, anxiety, depression, and opioid use, highlighting the central role of sleep within the cluster of postoperative negative symptoms.<sup>13</sup> The relationship between psychoactive

**Table 1** Clinical Studies of Sleep and Pain in Surgical and Related Populations

Authors	Type of Research	Type of Surgery	Type of Anesthesia	N	F/M	Sleep Measurement	Pain Measurement	Sleep→Pain	Pain→Sleep	Main Result
Stoop et al <sup>5</sup>	Quantitative/ Cross-sectional	All surgical subspecialties, excluding neurosurgical, cardiothoracic or orthopaedic patients	Not specified	733	518% male	PROMIS	NRS	N/A	Association reported	Sleep disturbances were prevalent in 64.1% of patients. Severe sleep disturbances were more common in patients with low socioeconomic status
Bartosiak et al <sup>6</sup>	Systematic Review	Knee osteoarthritis (KOA) and Total Knee Arthroplasty (TKA)	General vs neuraxial/regional	N/A	N/A	PSQI, PROMIS, ISI, ESS, objective measures (actigraphy, PSG)	Not specified	N/A	Yes	Sleep disturbances are prevalent in KOA and post-TKA patients, with up to 81% experiencing at least weekly sleep maintenance difficulties. Sleep quality often worsens in the first 6 weeks post-TKA but recovers to baseline or better by 3–6 months
Yang et al <sup>7</sup>	Quantitative/ Cross-sectional	Elective surgery, non-neurosurgical patients	Not specified	400	453% male	PSQI	NRS	N/A	Association reported	Postoperative sleep disturbances were classified into three latent profiles: mild (35.0%), moderate (44.2%), and severe (20.8%). High BMI, longer anesthesia duration, higher pain, and anxiety were significant predictors of moderate/severe sleep disturbance
Büyükyılmaz et al <sup>8</sup>	Qualitative descriptive	Orthopedic surgery	Not specified	75	49/26	McGill Pain Questionnaire (MPQ-SF), PSQI	VAS	N/A	Yes	Identified pain as the primary factor (45%) affecting postoperative sleep quality
Giordano et al <sup>9</sup>	Quantitative empirical	Total knee/hip arthroplasty	Not specified	197	95/102	PROMIS	DVPRS	N/A	Yes	Peripheral nerve blocks improved sleep quality indirectly by reducing pain
Koffel et al <sup>10</sup>	Quantitative empirical	Chronic pain patients (non-surgical)	Not applicable	250	Not Reported (Veteran cohort, likely majority Male)	Self-report questionnaire-es	BPI, PROMIS	N/A	Yes	Changes in pain predicted subsequent changes in sleep complaints
Edwards et al <sup>11</sup>	Quantitative empirical	General population (non-surgical)	Not applicable	971	Not Reported	Self-reported sleep duration	5-point scale	Yes	N/A	Both short (<6h) and long (>9h) sleep duration associated with increased next-day pain frequency
Creameans-Smith et al <sup>12</sup>	Quantitative empirical	Total knee replacement	Not specified	110	Not Reported	PSQI	AIMS, WOMAC	Yes	N/A	Postoperative sleep disruption mediated the relationship between early pain and later functional limitations

Azizoddin et al <sup>13</sup>	Prospective longitudinal study	Breast cancer surgery	General, regional	259	259/0 (All Female)	PROMIS	BCPQ	Yes	Yes	Postoperative sleep disturbance correlated with higher pain severity, anxiety, depression, and opioid use
Mamie et al <sup>14</sup>	Quantitative empirical	Abdominal or orthopedic surgery	Not specified	449 (304)	Not Reported	Questionnaire	VAS	N/A	N/A	Chronic sleep difficulty was the strongest predictor of postoperative pain at rest
Wright et al <sup>15</sup>	Quantitative empirical	Breast surgery	Not specified	24	24/0 (All Female)	Actigraphy	Brief Pain Inventory	N/A	N/A	Low sleep efficiency the night before surgery predicted more severe postoperative pain
Orbach-Zinger et al <sup>16</sup>	Observational study	Cesarean delivery	Spinal anesthesia	245	245/0 (All Female)	PSQI	VNPS	Yes	N/A	Poor preoperative sleep quality predicted higher postoperative pain intensity and analgesic requirements
Bjurström et al <sup>17</sup>	Cohort study	Groin hernia surgery	Not specified	2084	1130/954	Questionnaire	BPI-sf	Yes	N/A	Preoperative sleep problems predicted chronic pain risk up to 5 years postoperatively
Luo et al <sup>18</sup>	Prospective cohort study	Total joint arthroplasty	Not specified	994	Not Reported	PSQI, ESS	VAS	Yes	N/A	Preoperative sleep parameters correlated with pain, function, and hospital stay duration
Ho et al <sup>19</sup>	Predictive model	Gynecological surgery	General anesthesia	123	123/0 (All Female)	ISI, HRV	NRS	Yes	N/A	Combined sleep quality and HRV metrics effectively predicted postoperative moderate-to-severe pain

**Abbreviations:** PSQI, Pittsburgh Sleep Quality Index; PROMIS, Patient-Reported Outcomes Measurement Information System; ISI, Insomnia Severity Index; HRV, Heart Rate Variability; VAS, Visual Analog Scale; DVPRS, Defense and Veterans Pain Rating Scale; BPI, Brief Pain Inventory; BCPQ, Breast Cancer Pain Questionnaire; VNPS, Verbal Numerical Pain Scale; NRS, Numerical Rating Scale; AIMS, Arthritis Impact Measurement Scales; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ESS, Epworth Sleepiness Scale; N/A, Not assessed.

substance use and sleep disturbance extends beyond surgical populations. Large-scale epidemiological studies demonstrate that even single use of opioids or sedatives is independently associated with poor sleep quality, reduced sleep efficiency, and impaired daytime function.<sup>21,22</sup> These findings suggest that opioid use may both result from and exacerbate postoperative sleep disturbance, creating a complex bidirectional relationship that warrants careful consideration in pain management strategies.

## Preoperative Sleep Disturbance is a Significant Predictor of Acute and Chronic Postoperative Pain

The most clinically proactive finding is that pre-existing sleep problems are an independent risk factor for predicting adverse postoperative pain outcomes. This view has been confirmed across various types of surgery. The early work of Mamie et al identified chronic sleep difficulty as the strongest predictor of postoperative pain at rest.<sup>14</sup> Subsequently, Wright et al found that low sleep efficiency the night before breast cancer surgery predicted more severe pain during the first postoperative week.<sup>15</sup> Similarly, Orbach-Zinger et al, in a study of women undergoing planned cesarean delivery, showed that those with poor preoperative sleep quality experienced significantly higher pain intensity within the first 24 hours postoperatively and required additional analgesia more frequently.<sup>16</sup> Recent research has further revealed its impact on long-term outcomes. Bjurström et al, in patients undergoing groin hernia surgery, found that preoperative sleep problems not only predicted chronic pain at 12 months postoperatively but also the risk of persistent pain at a median follow-up of 5 years.<sup>17</sup> Studies by Luo et al and Bjurström et al in patients undergoing total joint arthroplasty further indicated that preoperative sleep disturbances were also associated with poorer joint function, longer hospital stays, and higher opioid consumption postoperatively.<sup>18,23</sup> The latest research, such as that by Ho et al, is attempting to combine preoperative sleep quality (eg., Insomnia Severity Index) with intraoperative physiological indicators (eg., heart rate variability) to develop more accurate predictive models for postoperative pain, signaling a move towards personalized and precision medicine in this field.<sup>19</sup>

## Hyperalgesia Induced by Experimental Sleep Deprivation

Experimental sleep deprivation, as a controlled research method, is widely used to investigate the mechanisms by which sleep loss affects pain perception. Experimental, observational, and meta-analytic evidence have elucidated the effects of sleep deprivation on pain (for details, see [Table 2](#)).

### Early Studies: Establishing the Basic Impact of Sleep Deprivation on Pain Perception

Early research primarily focused on the effects of total sleep deprivation on pain perception in healthy populations. For example, Larson and Carter, in their study, they found that 24 hours of total sleep deprivation significantly increased pain ratings in healthy subjects during the cold pressor test, but no gender differences were observed.<sup>25</sup> This study systematically evaluated the impact of TSD on clinically relevant pain induced by sustained cold stimulation for the first time, providing an important experimental paradigm for subsequent research.

In the same year, Schuh-Hofer et al used the standardized Quantitative Sensory Testing protocol from the German Research Network on Neuropathic Pain to comprehensively assess the effects of one night of TSD on multimodal nociception.<sup>24</sup> The study found that TSD significantly reduced thresholds for heat, mechanical, and cold pain, while non-nociceptive sensory functions remained unaffected. This suggests that TSD-induced hyperalgesia selectively enhances the nociceptive system.

### Mechanistic Exploration: From Subjective Pain to Neurophysiological Mechanisms

As research advanced, scholars began to investigate the neurobiological mechanisms underlying the effects of sleep deprivation on pain. Matre et al combined time-frequency electroencephalography analysis and found that sleep restriction increased the magnitude of pain-evoked EEG responses, whereas no changes were observed in the time-domain N2P2 amplitude.<sup>26</sup> This indicated that traditional ERP analyses might underestimate the impact of sleep deprivation on pain-related neural activity, and time-frequency analysis offered a new perspective for revealing its neural mechanisms.

**Table 2** Experimental and Observational Studies on the Effects of Sleep Deprivation on Pain Perception

Authors	Type of Research	N	F/M	Design	Sleep Measurement	Pain Measurement	Sleep→Pain	Pain→Sleep	Main Result
Schuh-Hofer et al <sup>24</sup>	Experimental QST	14	6/8	Randomized crossover (TSD vs. HS)	Actigraphy, Sleep Diary	QST	Yes	N/A	One night of TSD promotes generalized hyperalgesia, lowering heat, mechanical, and cold pain thresholds.
Larson & Carter <sup>25</sup>	Experimental	30 (15/15 planned)	15/15	Randomized crossover (TSD vs. NS)	/	Cold Pressor Test (CPT), Modified Borg Scale	Yes	N/A	24-hour TSD significantly increased perceived pain intensity during CPT. No significant gender differences were found.
Matre et al <sup>26</sup>	Experimental EEG	21	Not specified	Randomized crossover (SR vs. HS)	Polysomnography (PSG)	Electrical stimulation, Pressure Pain Threshold (PPT), VAS	Yes	N/A	Sleep restriction (SR) increased pain sensitivity to electrical stimuli and pressure, and enhanced pain-evoked EEG responses in time-frequency analysis.
Irwin et al <sup>27</sup>	Randomized Clinical Trial	95	~46/49	Assessor-blinded, crossover (FA vs. US)	Polysomnography (PSG)	Heat Pain Threshold (hPTH)	Yes	N/A	Sleep disruption (FA) heightened pain sensitivity, mediated by both N3 sleep reduction (25%) and cellular inflammation (19%).
Stroemel-Scheder & Lautenbacher <sup>28</sup>	Experimental	21	21/0	Within-subject (Baseline, TSD, RS)	Polysomnography (PSG)	Pressure Pain Thresholds (PPTs), Temporal Summation (TSP), Conditioned Pain Modulation (CPM)	Yes	N/A	Recovery sleep (RS) reversed TSD-induced hyperalgesia (lowered PPTs). Sleep efficiency and slow-wave sleep predicted recovery.
Jansson-Fröjmark & Boersma <sup>29</sup>	Prospective Cohort	1,746	Not specified	Longitudinal (1-year follow-up)	Basic Nordic Sleep Questionnaire, Uppsala Sleep Inventory	Self-reported pain (back, neck, shoulder)	Yes	N/A	Pain predicted the onset and persistence of insomnia, but insomnia only predicted the persistence of pain, not a fully bidirectional relationship.
Chang et al <sup>30</sup>	Systematic Review & Meta-Analysis	699 healthy, 47 chronic pain	Varies by study	Systematic review of RCTs and quasi-experimental studies	Various (SD protocols)	Various (threshold, tolerance, intensity)	Yes	N/A	Total and partial SD significantly increased pain sensitivity in healthy individuals. Evidence in chronic pain patients is limited but suggests increased spontaneous pain.

**Abbreviations:** F/M, Female/Male; QST, Quantitative Sensory Testing; TSD, Total Sleep Deprivation; HS, Habitual Sleep; NS, Normal Sleep; FA, Forced Awakening; US, Uninterrupted Sleep; RS, Recovery Sleep; EEG, Electroencephalography; VAS, Visual Analog Scale; OR, Odds Ratio; N/A, Not assessed.

Irwin et al further demonstrated in a randomized clinical trial that sleep disruption not only enhanced pain sensitivity but also mediated this effect through dual pathways: reduction in N3 sleep and activation of cellular inflammation. Specifically, N3 sleep accounted for 25.0% of the mediation, inflammation for 19.0%, and the dual mediation pathway accounted for 34.9%.<sup>27</sup> This study was the first to quantify the mediating roles of sleep architecture and inflammation in pain perception within a causal framework, providing mechanistic evidence for the “sleep-inflammation-pain axis.”

## From Healthy Populations to Clinical Ample: Expansion of Research Subjects

As experimental paradigms matured, researchers began to shift their focus to chronic pain patients. Chang et al, in a systematic review, noted that both total and partial sleep deprivation significantly exacerbated spontaneous pain intensity in individuals with chronic pain, but their effects on pain thresholds and tolerance remained unclear.<sup>30</sup> This study emphasized the need to distinguish the effects of different sleep deprivation paradigms on pain outcomes and called for the establishment of standardized experimental protocols.

Jansson-Fröjmark and Boersma, in a prospective study, found that in the general population, pain predicted the onset and persistence of insomnia symptoms, whereas insomnia symptoms were only associated with the persistence of pain, not its onset, partially refuting the hypothesis of a fully bidirectional relationship.<sup>29</sup>

## The Interventional Value of Recovery Sleep

In recent years, researchers have begun to explore the reversibility of pain perception through recovery sleep. Stroemel-Scheder and Lautenbacher found that one night of recovery sleep significantly reversed the decrease in pain thresholds caused by total sleep deprivation, with sleep efficiency and slow-wave sleep duration being important predictors of pain recovery. This provides experimental evidence for intervening in pain by improving sleep quality.<sup>28</sup>

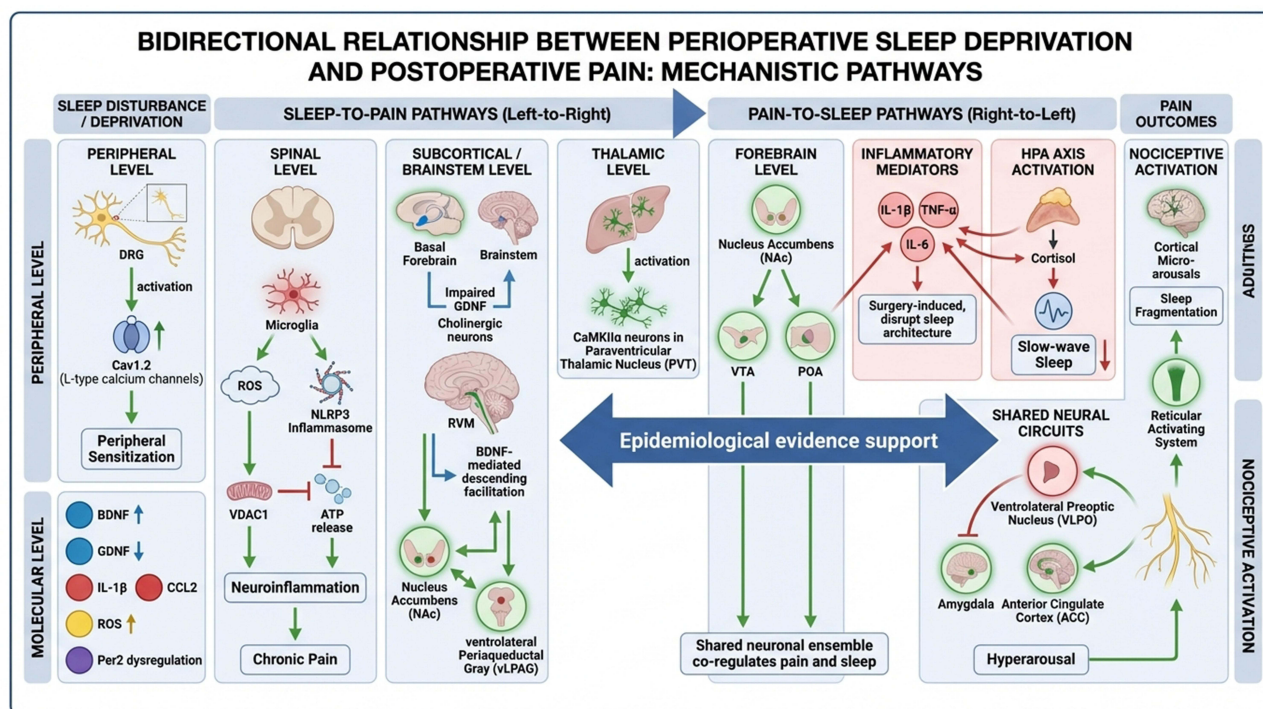
In conclusion, the academic community generally agrees that: experimental sleep deprivation can induce hyperalgesia; its mechanisms involve multiple pathways including altered central nervous system processing and inflammatory activation; and recovery sleep exhibits some degree of pain-reversing effects. However, the following issues remain controversial: the similarities and differences in the effects of various sleep deprivation paradigms (total, partial, selective, and fragmented) on pain; the differential impacts of sleep deprivation between chronic pain patients and healthy populations; and the interactive effects between sleep architecture and inflammation in mediating pain mechanisms. Future research should further deepen efforts in standardizing experimental paradigms, integrating multi-mechanism analyses, and developing individualized intervention strategies to advance this field toward precision sleep medicine and pain management.

## The Mechanism Underlying the Interaction Between Sleep and Pain Has Not Been Fully Elucidated

Sleep and pain are interrelated physiological processes, with sleep disorders and chronic pain frequently co-occurring in clinical settings. However, the underlying neurobiological mechanisms remain incompletely understood. In recent years, advances in multimodal techniques, molecular biology, and neural circuit research have revealed the effects of sleep deprivation—particularly perioperative sleep deprivation—on pain sensitivity, chronic pain development, and brain function across multiple levels, from the periphery and spinal cord to subcortical and cortical regions. The mechanism of the bidirectional relationship between perioperative sleep deprivation and postoperative pain is shown in [Figure 2](#).

## Peripheral and Spinal Mechanisms: L-Type Calcium Channels, Microglial Activation, and Oxidative Stress

Early research focused on the effects of sleep deprivation on peripheral pain transmission pathways, such as the dorsal root ganglion (DRG). Li et al found that perioperative sleep deprivation upregulates the expression and activity of L-type calcium channels (Cav1.2) in the DRG of rats, thereby prolonging postoperative pain recovery. This effect could be reversed using the calcium channel blocker nifedipine or by knocking down Cav1.2, suggesting that L-type calcium channels are important peripheral targets through which sleep deprivation prolongs pain.<sup>31</sup> Subsequently, Huang et al



**Figure 2** The mechanistic pathways of bidirectional relationship between perioperative sleep deprivation and postoperative pain.

further demonstrated at the spinal level that sleep deprivation increases reactive oxygen species (ROS) levels, activates microglia and the NLRP3 inflammasome, and leads to DNA damage and hyperalgesia. These changes could be reversed by the ROS inhibitor PBN.<sup>32</sup> Wei et al focused on the voltage-dependent anion channel 1 (VDAC1) signaling in microglia, showing that sleep deprivation promotes VDAC1 oligomerization, increases ATP release and inflammatory factor (IL-1 $\beta$ , CCL2) expression, thereby driving the transition from acute to chronic pain. Inhibiting VDAC1 with DIDS or its oligomerization with VBIT-4 produced analgesic effects similar to those of the microglial inhibitor minocycline.<sup>33</sup> Together, these studies elucidate a cascade of mechanisms—involving ion channels, oxidative stress, and neuroimmune responses—through which sleep deprivation promotes pain chronicity at the peripheral and spinal levels.

## Brain Region and Circuit Regulation: NAc-vLPAG Functional Connectivity, Basal Forebrain Cholinergic System, and PVT Nucleus

As research has advanced, attention has shifted to the impact of sleep deprivation on central pain modulation networks. Guo et al, using multimodal techniques (fMRI, c-Fos, electrophysiology), found that preoperative acute sleep deprivation (ASD) inhibits functional connectivity and neuronal activity between the nucleus accumbens (NAc) and the ventrolateral periaqueductal gray (vLPAG), leading to postoperative hyperalgesia.<sup>34</sup> Sun et al further revealed that a population of D1 neurons in the NAc co-regulates pain and sleep. Projections from these neurons to the ventral tegmental area (VTA) and preoptic area (POA) specifically modulate pain responses and sleep architecture, respectively, providing a unified neural ensemble basis for pain-sleep comorbidity.<sup>35</sup> At the subcortical level, Wang et al demonstrated that perioperative sleep deprivation reduces glial cell line-derived neurotrophic factor (GDNF) signaling in basal forebrain cholinergic neurons, leading to neuronal apoptosis and autophagy dysfunction, which promotes chronic postoperative pain. Overexpression of GDNF reversed these effects.<sup>36</sup> Li et al focused on the paraventricular thalamic nucleus (PVT), showing that rapid eye movement sleep deprivation (REMSD) activates CaMKII $\alpha$  neurons in the PVT, prolonging postoperative pain duration. Chemogenetic inhibition of these neurons abolished the pain-promoting effects of REMSD.<sup>37</sup> Collectively, these studies progressively map a distributed brain network—spanning the NAc, vLPAG, basal forebrain, and PVT—clarifying how sleep deprivation exacerbates pain by disrupting descending pain modulation and sleep-wake circuits.

## Molecular and Signaling Pathways: BDNF, GDNF, and Circadian Genes

At the molecular level, Xue et al were the first to propose that paradoxical sleep deprivation enhances brain-derived neurotrophic factor (BDNF) expression in the rostral ventromedial medulla (RVM), activating descending facilitation pathways and exacerbating incision-induced hyperalgesia. This effect could be reversed by lesioning the dorsolateral funiculus or administering BDNF antibodies.<sup>38</sup> Russell et al approached the issue from a circadian rhythm perspective, finding that knockout of the circadian clock gene *Per2* disrupts corticosterone secretion rhythms, leads to hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and induces depressive-like behaviors and deficits in startle responses. This suggests that circadian rhythm disruption may exacerbate pain-affective comorbidity via neuroendocrine pathways.<sup>39</sup> These findings, together with research on GDNF signaling and inflammatory pathways, collectively construct a molecular network through which sleep deprivation influences pain, encompassing neurotrophic factors, circadian rhythms, stress hormones, and inflammatory mediators.<sup>32,33,36</sup>

The interaction between sleep and pain involves multiple levels, including peripheral sensitization, spinal immune activation, brain network remodeling, and molecular signaling dysregulation. From early focus on local channels and inflammatory responses to recent emphasis on distributed brain circuits and neurotrophic factor systems, the field is gradually progressing from phenomenological description to mechanistic integration. Future research should adopt cross-level, cross-species strategies to deeply elucidate the neurobiological basis of sleep-pain comorbidity and provide novel insights for developing targeted interventions.

## Pain-to-Sleep Mechanisms: Nociceptive Activation, Inflammation, and Stress-Induced Sleep Fragmentation

While the preceding sections detail how sleep deprivation exacerbates pain, the reciprocal pathway—how postoperative pain disrupts sleep architecture—is equally important for understanding the bidirectional relationship. Pain interferes with sleep through multiple interconnected mechanisms involving nociceptive arousal, neuroinflammation, and stress system activation.

**Nociceptive arousal and sleep fragmentation.** Ascending nociceptive inputs during sleep activate the ascending reticular activating system and trigger cortical micro-arousals, leading to sleep fragmentation and reduced slow-wave sleep. Experimental studies in rodents have shown that nociceptive stimulation during sleep increases the frequency of sleep-wake transitions and suppresses NREM and REM sleep maintenance. In surgical patients, nighttime pain is strongly correlated with the number of awakenings and reduced sleep efficiency.<sup>8</sup>

**Inflammatory mediators as sleep-modulating signals.** Surgical trauma induces systemic and central neuroinflammation, with elevated pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6. These cytokines are well-established somnogenic regulators: IL-1 $\beta$  and TNF- $\alpha$  promote NREM sleep under physiological conditions but, when chronically elevated, disrupt sleep architecture and reduce sleep quality. In the postoperative setting, persistent pain maintains inflammatory signaling, creating a feedback loop where inflammation both amplifies pain and fragments sleep.<sup>27</sup>

**HPA axis activation and stress hormone dysregulation.** Pain is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol (corticosterone in rodents) release. Circadian disruption of glucocorticoid secretion—as seen in patients with poorly controlled postoperative pain—impairs sleep continuity and reduces slow-wave sleep. Russell et al demonstrated that disruption of the circadian gene *Per2* leads to HPA axis dysfunction and behavioral abnormalities, suggesting a molecular link between pain-induced stress and sleep disruption.<sup>39</sup>

**Shared neural circuits: Pain and sleep regulatory nuclei overlap.** Brain regions involved in pain processing—such as the parabrachial nucleus, thalamus, and insula—project to sleep-regulatory centers including the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamus. Nociceptive inputs can directly inhibit VLPO sleep-promoting neurons, reducing sleep pressure and promoting wakefulness. Conversely, pain-induced activation of the amygdala and anterior cingulate cortex enhances hyperarousal, further disrupting sleep continuity.

**Clinical correlation.** The clinical relevance of these mechanisms is supported by studies demonstrating that effective pain control—such as peripheral nerve blocks or multimodal analgesia—improves sleep quality postoperatively.<sup>9,20</sup> This provides indirect evidence that pain drives sleep disruption through identifiable neurobiological pathways.

## Conclusion

### Limitations of Current Research

Several methodological limitations should be acknowledged in the context of perioperative sleep and pain research. First, heterogeneity in sleep assessment tools across studies—ranging from subjective scales (PSQI, ISI) to objective measures (actigraphy, polysomnography)—limits cross-study comparability in surgical populations. Second, mechanistic insights derive predominantly from preclinical models, creating translational gaps between rodent studies and human postoperative pain. Third, limited follow-up durations in most clinical studies of surgical patients fail to capture the long-term evolution of sleep–pain interactions and the transition to chronic postsurgical pain. Fourth, inadequate control for confounders specific to the perioperative setting (anxiety, depression, opioid use, surgical factors, anesthetic technique) may introduce bias in effect estimates.

### Unanswered Questions in Perioperative Sleep-Pain Research

Key questions remain unresolved in the perioperative context: (1) Do different sleep deprivation patterns (total vs. partial, N3 reduction vs. REM deprivation) exert differential effects on postoperative pain outcomes? (2) What is the role of sex differences in sleep–pain interactions among surgical patients? (3) What is the critical perioperative time window during which sleep disturbance most strongly promotes the transition from acute to chronic postsurgical pain? (4) How do peripheral and central mechanisms interact in surgical patients—does peripheral sensitization from surgical trauma trigger central changes, or do preoperative sleep disturbances prime central pain circuits before surgery?

### Controversies in the Field

Three major controversies persist in perioperative sleep–pain research. First, causality direction: Is sleep disturbance a cause or consequence of chronic postsurgical pain? While Jansson-Fröjmark and Boersma<sup>29</sup> found in a general population that pain predicted insomnia onset but not vice versa, numerous perioperative studies demonstrate that preoperative sleep disturbance predicts postoperative pain outcomes, suggesting that the causal relationship may differ between surgical and non-surgical contexts. Second, reversibility: Can perioperative sleep optimization completely reverse sleep deprivation-induced hyperalgesia in surgical patients? Evidence from recovery sleep studies in healthy volunteers shows partial reversal with substantial individual variability<sup>34</sup>, but data in postoperative populations remain limited. Third, mechanism dominance: Are central or peripheral mechanisms primary in mediating the effects of perioperative sleep deprivation on postsurgical pain? Recent discoveries of peripheral L-type calcium channels<sup>35</sup> and spinal microglial VDAC1 signaling<sup>37</sup> challenge traditional “central dominance” views and suggest that multi-level interventions may be required.

### Future Directions for Perioperative Research

Based on the perioperative focus of this review, we propose six research priorities tailored to surgical populations:

1. Standardized longitudinal perioperative studies: Implement uniform sleep assessment tools (PSQI + actigraphy) from preoperative baseline through acute recovery to chronic follow-up (6–12 months), with multimodal data collection including inflammatory markers and neuroimaging to identify predictors of chronic postsurgical pain.
2. Translational research with surgical relevance: Develop clinically relevant animal models that combine postoperative pain with chronic sleep fragmentation, rather than acute sleep deprivation alone, to better model the clinical reality of surgical patients.
3. Sex-specific mechanisms in surgical populations: Ensure adequate female representation in perioperative clinical studies and preclinical surgical models to elucidate hormonal modulation of sleep–pain circuits in the context of surgical trauma and recovery.
4. Perioperative sleep-targeted interventions: Conduct randomized controlled trials in surgical patients targeting sleep improvement through preoperative optimization (CBT-I), intraoperative strategies (anesthetic technique), and

postoperative interventions (pharmacotherapy, neuromodulation) to establish causality and therapeutic potential for improving postsurgical pain outcomes.

5. Multi-omics integration in surgical cohorts: Combine transcriptomics, proteomics, and neuroimaging in well-characterized perioperative cohorts to identify key molecular targets and brain networks mediating the transition from acute to chronic postsurgical pain.
6. Mechanism-based therapies for perioperative use: Explore targeted interventions with potential for perioperative application, including L-type calcium channel blockers, ROS inhibitors, VDAC1 inhibitors, GDNF enhancement, PVT modulation, and slow-wave sleep restoration, with careful consideration of safety in surgical patients.

While the bidirectional relationship between sleep and pain is well-established in general populations, its specific manifestations in the perioperative context involve unique considerations related to surgical trauma, anesthesia, and the postoperative recovery trajectory. Mechanistic understanding of how perioperative sleep deprivation influences chronic postsurgical pain remains incomplete, but recent advances have identified promising peripheral, spinal, and central targets for intervention. Addressing the limitations, unanswered questions, and controversies outlined above through rigorous translational research focused on surgical populations will pave the way for mechanism-based perioperative interventions that improve postoperative recovery and reduce the burden of chronic postsurgical pain.

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## Disclosure

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