The bidirectional relationship between sleep and pain

DAVID HILLMAN MB BS, FANZCA, FRCPE, FRACP(Hon)

Although it is well understood that uncontrolled pain is a source of sleep disturbance, disturbed sleep can also aggravate pain. Assessment of patients with pain should include consideration of this bidirectional relationship, including treatment of both the pain, with appropriate caution around the use of opioid analgesics, and the disturbed sleep.

Key points

- **Pain and sleep have a bidirectional relationship: pain disturbs sleep, and disturbed sleep exacerbates pain.**
- **Treating sleep disorders has positive effects on pain symptoms, while treatment of pain with opioid analgesics can have positive and negative effects on sleep.**
- **Chronic opioid use is often associated with disordered breathing during sleep.**
- **Continuous positive airway pressure therapy may be indicated when disordered breathing during sleep is obstructive, whereas adaptive servo-ventilation therapy may have a role if central sleep apnoea is present.**
- **Some common mechanisms are involved, with central sensitisation known to have a role in both the pathogenesis of pain and disturbed sleep in patients with fibromyalgia.**

PAIN MANAGEMENT TODAY 2016; 3(2): 30-31

Professor Hillman is a Clinical Professor in the Department of Pulmonary Physiology and Sleep Medicine at Sir Charles Gairdner Hospital, Perth, WA.

Sleep and pain have a bidirectional relationship: pain disrupts sleep, and disrupted sleep lowers the threshold to pain. Further, treatment of sleep disorders can increase pain thresholds, while treatment of pain can benefit sleep, although opioid analgesia has potential harms. Psychological factors also interact with the neurobiological links between sleep and pain. Depression is commonly associated with both chronic pain and disturbed sleep, and, in turn, common sleep disorders, such as obstructive sleep apnoea and insomnia, are associated with depressive symptoms.[1] Catastrophising about pain, with its accompanying ruminative thoughts, disturbs both pain perception and sleep. It is possible that disturbed sleep is the medium through which such catastrophising aggravates pain.[2] Hence, treatments need to be directed at both the physical and psychological factors that underpin these complex links between disturbed sleep and pain. Importantly, such links appear to relate to myriad causes of pain and disturbed sleep, including both clinical sleep disorders and inadequate sleep through lifestyle choice or necessity, such as shift work. These interrelationships deserve closer examination.

A bidirectional relationship

Pain disturbs sleep

The results of many studies have objectively demonstrated that pain disturbs sleep. A recent systematic review showed consistent evidence of disturbed sleep in patients with chronic low back pain.[3] Both sleep duration and quality suffer: it takes longer to achieve sleep, and dissatisfaction with sleep increases. Daytime functioning is also adversely affected by these sleep problems. One study found clinically significant insomnia in more than half of patients with chronic back pain, while in another study almost 90% of patients seeking treatment in a pain clinic had at least one sleep complaint.[4,5] In patients with fibromyalgia, where central sensitisation is a core issue, sleep disturbance is ubiquitous.[6]

Disturbed sleep can aggravate pain

Just as pain can disturb sleep, so can disturbed sleep aggravate pain. One night of total sleep deprivation has been shown to increase pain sensitivity to heat, cold, blunt pressure and pinprick in healthy people.[7]

A study found that self-reported short sleepers (less than 6.5 hours a night) had reduced thresholds to the effects of noxious stimuli, such as capsaicin.[8] Another study found that restricting healthy volunteers to four hours' sleep a night for a series of nights was associated with increased pain-related complaints.[9] One night of such sleep restriction exacerbated pain in patients with rheumatoid arthritis,[10] while disturbed sleep before breast surgery has been associated with postoperative pain.[11] The pain and disturbed sleep associated with fibromyalgia are manifestations of central sensitisation and are likely to exacerbate each other.[12] Interestingly, and somewhat contrary to the many examples of the aggravating effect of disturbed sleep on pain, there is some evidence to suggest that hypoxaemia during sleep can increase analgesic sensitivity to opioids.[13]

Treatment of sleep disorders and pain

Treating sleep disorders can reduce pain symptoms

Increasing time in bed for healthy, mildly sleepy people has been shown to decrease pain sensitivity to radiant heat.[14] Use of hypnotic drugs appears to reduce both insomnia and pain symptoms in patients with rheumatoid arthritis[15] and can also reduce pain and analgesic requirements after knee surgery.[16] A study of patients with mucositis secondary to haematological malignancies found that sleep and pain scores improved with the use of hypnotics.[17] Melatonin has been shown to have both sedative and antinociceptive effects in patients with temporomandibular disorders.[18] The aggravating effects of sleep loss on pain perception are reversed by restoration of normal sleep.[14]

Treating pain has benefits for sleep, but opioid use requires caution

Although relief of pain has obvious benefits for sleep quality, use of opioid analgesics requires caution. In 1997, the American Academy of Pain Medicine and American Pain Society issued a joint statement in which they said: 'It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.'[19] More aggressive pain management followed, with a massive increase in opioid prescriptions and an associated threefold increase in mortality rate by 2003 in the United States.[20,21] However, the basic tenet behind the 1997 statement was flawed, as they failed to consider the effects of opioids on ventilation during sleep.

Opioids have several effects that are relevant in this regard. Acutely, opioids depress:

- ventilatory drive, in response to both hypercapnia and hypoxia[22,23]
- pharyngeal reflexes responsible for stabilising the upper airway during inspiration[24]
- arousal responses to upper airway obstruction, hypoventilation and hypoxaemia[3]
- volitional modulation of respiration[25]
- pharyngeal dilator muscle activity, through their effect on the hypoglossal and related nuclei.[26]

These changes occur in a dose-related manner and can cause hypoventilation, upper airway obstruction and failure to arouse, especially in patients with predispositions to these problems. Patients with obstructive sleep apnoea or a tendency to hypoventilation because of obesity, neuromuscular disease or advanced lung disease and those with obtunded consciousness are particularly vulnerable. The problems are aggravated by sleep, hypercapnia and other sedatives. Vulnerable patients are of particular concern in the early postoperative period, when opioids are being administered.

Chronic opioid use

With chronic use of opioids, some tolerance to their central depressant effects develops. However, there is evidence to suggest opioids have contrasting effects on peripheral carotid body and central medullary chemoreceptor responses, with augmentation of hypoxic responses and blunting of hypercapnic responses.[27] This is a recipe for breathing instability, and periodic or ataxic breathing is seen in 30 to 70% of patients receiving chronic opioid treatment.[28] As with other forms of breathing disturbance, sleep is a vulnerable time, with breathing periodicity being much more obvious as the non-specific stimulatory effects of wakefulness are lost. This periodic breathing can, in turn, disrupt sleep, either because of arousals triggered by obstructive events that can occur during the hypoventilatory phase (when drive to both the respiratory pump muscles and the upper airway is reduced) or because of arousals precipitated during the hyperventilatory phase of the cycle.[29]

Positive airway pressure therapies can help. Continuous positive airway pressure therapy is useful if the problem is predominantly obstructive, whereas adaptive servo-ventilation therapy is helpful if periodicity and sleep disturbance persist despite relief of upper airway obstruction. Adaptive servo-ventilation provides variable pressure support – increasing during hypopnoea and reducing with hyperpnoea – having the effect of dampening out the oscillations in the breathing pattern and the associated sleep disruption.[30]

Conclusion

Although it is well understood that uncontrolled pain is a source of sleep disturbance, it is clear that the reverse is also true: disturbed sleep can aggravate pain. Assessment of patients with pain – acute or chronic – is incomplete without consideration of its impacts on sleep and the effect of disturbed sleep on the pain. This should extend to identifying other sources of sleep disturbance apart from those directly attributed to pain, and considering treatment for both the pain and the disturbed sleep. In using opioid analgesics, careful thought must be given to their potentially deleterious effects on breathing during sleep, with both acute and chronic use. PMT

References

A list of references is included in the website version of this article (www.painmanagementtoday.com.au).

COMPETING INTERESTS: None.

The bidirectional relationship between sleep and pain

DAVID HILLMAN MB BS, FANZCA, FRCPE, FRACP(Hon)

References

1. Edwards C, Mukherjee S, Simpson L, Palmer LJ, Almeida OP, Hillman DR. Depressive symptoms before and after treatment of obstructive sleep apnea in men and women. J Clin Sleep Med 2015; 11: 1029-1038.
2. Lautenbacher S. Pain, sleeping problems and their many relatives. Pain 2012; 153: 1138.
3. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. Clin J Pain 2011; 27: 169-181.
4. Tang NK, Wright KJ, Salkovskis PM. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. J Sleep Res 2007; 16: 85-95.
5. McCracken LM, Iverson GL. Disrupted sleep patterns and daily functioning in patients with chronic pain. Pain Res Manag 2002; 7: 75-79.
6. Theadom A, Cropley M, Humphrey KL. Exploring the role of sleep and coping in quality of life in fibromyalgia. J Psychosom Res 2007; 62: 145-151.
7. 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: 1613-1621.
8. Campbell CM, Bounds SC, Simango MB, et al. Self-reported sleep duration associated with distraction analgesia, hyperemia, and secondary hyperalgesia in the heat-capsaicin nociceptive model. Eur J Pain 2011; 15: 561-567.
9. Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. Pain 2005; 119: 56-64.
10. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep 2012; 35: 537-543.
11. Wright CE, Bovbjerg DH, Montgomery GH, et al. Disrupted sleep the night before breast surgery is associated with increased postoperative pain. J Pain Symptom Manage 2009; 37: 352-362.
12. Serra E, Spaeth M, Carbonell J, et al. Development of the Fibromyalgia Burden Assessment: measuring the multifaceted burden of fibromyalgia. Clin Exp Rheumatol 2010; 28(6 Suppl 63): S87-S93.
13. Brown KA, Laferriere A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. Anesthesiology 2004; 100: 806-810; discussion 5A.
14. Roehrs TA, Harris E, Randall S, Roth T. Pain sensitivity and recovery from mild chronic sleep loss. Sleep 2012; 35: 1667-1672.
15. Walsh JK, Muehlbach MJ, Lauter SA, Hilliker NA, Schweitzer PK. Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. J Rheumatol 1996; 23: 245-252.
16. Tashjian RZ, Banerjee R, Bradley MP, Alford W, Fadale PD. Zolpidem reduces postoperative pain, fatigue, and narcotic consumption following knee arthroscopy: a prospective randomized placebo-controlled double-blinded study. J Knee Surg 2006; 19: 105-111.
17. Dimsdale JE, Ball ED, Carrier E, et al. Effect of eszopiclone on sleep, fatigue, and pain in patients with mucositis associated with hematologic malignancies. Support Care Cancer 2011; 19: 2015-2020.
18. Vidor LP, Torres IL, Custodio de Souza IC, Fregni F, Caumo W. Analgesic and sedative effects of melatonin in temporomandibular disorders: a double-blind, randomized, parallel-group, placebo-controlled study. J Pain Symptom Manage 2013; 46: 422-432.
19. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997; 13: 6-8.
20. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007; 3: 455-461.
21. Caravati EM, Grey T, Nangle B, Rolfs RT, Peterson-Porucznik CA. CDC: Increase in poisoning deaths caused by non-illicit drugs—Utah 1991–2003. MMWR 2005; 54: 3-6.
22. Ladd LA, Kam PC, Williams DB, Wright AW, Smith MT, Mather LE. Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypoxaemic conditions. Br J Clin Pharmacol 2005; 59: 524-535.
23. Lalley PM. Opioidergic and dopaminergic modulation of respiration. Respir Physiol Neurobiol 2008; 164: 160-167.
24. Santiago TV, Remolina C, Scoles V 3rd, Edelman NH. Endorphins and the control of breathing. Ability of naloxone to restore flow-resistive load compensation in chronic obstructive pulmonary disease. N Engl J Med 1981; 304: 1190-1195.
25. Pattinson KT, Governo RJ, MacIntosh BJ, et al. Opioids depress cortical centers responsible for the volitional control of respiration. J Neurosci 2009; 29: 8177-8186.
26. Hajiha M, DuBord MA, Liu H, Horner RL. Opioid receptor mechanisms at the hypoglossal motor pool and effects on tongue muscle activity in vivo. J Physiol 2009; 587: 2677-2692.
27. Teichtahl H, Wang D, Cunnington D, et al. Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. Chest 2005; 128: 1339-1347.
28. Paturi AK, Surani S, Ramar K. Sleep among opioid users. Postgrad Med 2011; 123: 80-87.
29. Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. Sleep 1997; 20: 654-675.
30. Hetzenecker A, Roth T, Birner C, Maier LS, Pfeifer M, Arzt M. Adaptive servo-ventilation therapy of central sleep apnoea and its effect on sleep quality. Clin Res Cardiol 2016; 105: 189-195.