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Might chronic opioid use impact sleep-disordered breathing and vice versa?

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COMMENTARY

Might chronic opioid use impact sleep-disordered breathing and vice versa?

Commentary on Mubashir T, Nagappa M, Esfahanian N, et al. Prevalence of sleep-disordered breathing in opioid users with chronic pain: a systematic review and meta-analysis. *J Clin Sleep Med*. 2020;16(6):961–969. doi:10.5664/jcsm.8392

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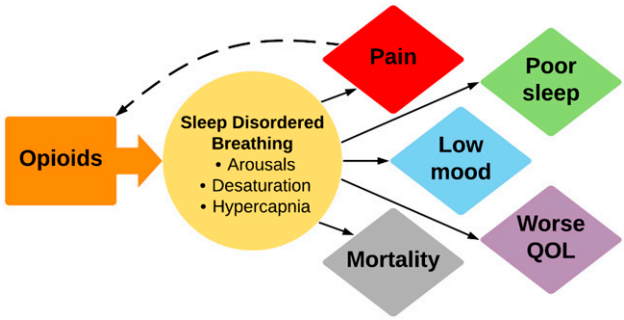
The use of opioids has gained considerable attention over the last decade based on their alarming impact on public health.[1] Although illicit use is widely known to carry substantial risk, opioid use under medical guidance has also been linked to adverse health outcomes, including persistent chronic pain, sleep disturbances, and excess mortality.[2] An important question is whether sleep disorders, including sleep-disordered breathing (SDB), might contribute to such effects. Physical pain can clearly worsen sleep, but in addition, evidence suggests that poor sleep seems to worsen pain.[3–5] In terms of SDB, some data suggest that pain thresholds seem to improve with continuous positive airway pressure treatment in those with obstructive sleep apnea.[6,7] Among those with chronic pain using opioids, data regarding the effect of SDB on pain are sparse.[8] However, given the effects of opioids on breathing, the possibility exists of a vicious cycle whereby opioids contribute to sleep disruption (by promoting obstructive sleep apnea and/or central sleep apnea), and impaired sleep worsens pain, leading to increased opioid use (**Figure 1**).[9] If this conjecture were true, one might argue that recognizing and addressing SDB may be an effective strategy for at least some patients who use opioids. SDB may also increase the risk of poor outcomes via established cardiometabolic, neurocognitive, and respiratory depressant pathways.[10] Understanding the prevalence and characteristics of SDB among those using opioids is vital toward defining the potential scope of this issue.

In this issue of the *Journal of Clinical Sleep Medicine*, Mubashir et al[11] report the results of a systematic review and meta-analysis of the prevalence of SDB among those using opioids for chronic pain. Their findings were based on 9 studies, in which they found an estimated prevalence of SDB of 91% among opioid users in sleep clinics and 63% in pain clinics, although the overall prevalence of SDB did not differ from those not using opioids. Central sleep apnea was found in 20–33% of opioid users, which was significantly higher than those not using opioids. Similarly, the apnea-hypopnea index was not substantially different in the presence of opioid use, but the central apnea index was higher than in the absence of opioids. Three studies reported on oximetry during sleep, with significantly higher percent sleep with saturation <90% in opioid users compared with nonusers (18% vs 0.1%). Last, 2 studies reported daytime hypercapnia in a substantial fraction of individuals using opioids.

Several points should be emphasized regarding the potential importance of opioids in SDB:

1. Although the study of Mubashir et al[11] did not clearly show opioids as an overall risk factor for SDB, the original studies have limitations, including mostly retrospective data and heterogeneous referral populations. In addition, there is a lack of key data on opioid preparation (ie, short vs long acting) and coadministered medications that might affect sleep and breathing. Overall, there is clearly a need for more prospective rigorous research examining the epidemiology of SDB among opioid users, an assertion supported by a recent American Academy of Sleep Medicine position statement.[12]
2. This study suggests that the prevalence of SDB is quite high, yet the consequences of SDB among opioid users remain to be established. The occurrence of sleep apnea (either central or obstructive) with opioids may result in sleep fragmentation, leading toward adverse health outcomes via a number of pathways. Similarly, desaturation or respiratory depression may also contribute toward serious cardiometabolic, neurocognitive, or respiratory complications. These issues would be best addressed by dedicated studies of opioid users, although attention to opioid use among all SDB studies should also provide useful information. Conversely, pain medicine clinicians might consider the established effects of SDB toward sleep disruption, mood, and impairments in daytime function. Recognizing and treating SDB has clear benefits for some individuals.
3. The pharmacology of opioids is complex, with varying effects that may affect SDB pathogenesis. Controller gain (chemoresponsiveness) may be reduced toward CO_2 but increased toward O_2,[13] whereas plant gain (efficiency of CO_2 excretion) may be increased.[14] Patients with chronic pain may be sedentary,

Figure 1—Model of the potential relationships between opioids, sleep-disordered breathing, and important outcomes.



Opioids may contribute to the pathogenesis of sleep-disordered breathing, contributing to arousals, desaturation, and hypercapnia. Pain, poor sleep, low mood, worse quality of life, and mortality have been linked to sleep-disordered breathing, and those using chronic opioids may be particularly at risk. There is potential for a feed-forward pathway in which opioid use contributes to sleep-disordered breathing, which might in turn lead to increased pain (potentially via sleep disruption or other mechanisms) and further opioid use, propagating a vicious cycle.

contributing to increased body weight, and opioids seem to have vasodilatory properties that could contribute to fluid accumulation and rostral shifts.[15,16] In contrast, unintended weight loss may be associated with opioid misuse. Thus, the effects of chronic opioids on upper airway anatomy may be complex. Moreover, studies indicate that opioids can impair hypoglossal motor neuron output, contributing to upper airway collapse among anatomically predisposed individuals.[17]

4. The apnea-hypopnea index may not capture the degree of respiratory abnormality induced by opioids. Many different breathing patterns have been reported with opioid use, including sustained hypoventilation, ataxic (Biot's) breathing, obstructive sleep apnea, and central sleep apnea. Thus, more detailed physiologic studies may be needed to characterize SDB adequately in this population and to interpret the study of Mubashir et al[11] rigorously.
5. Many studies regarding the effects of opioids on breathing have examined acute administration rather than chronic use, which may have substantially different pathophysiology. For example, respiratory control is known to have plasticity over time.[18,19]
6. Treatment of SDB in those using opioids can be a challenge. To the extent that opioids drive an individual's SDB, dose reduction may be helpful, although not always feasible. Treatment options include continuous positive airway pressure, noninvasive ventilation, adaptive servoventilation, and perhaps non–positive airway pressure therapies. Nonetheless, these therapies may not fully resolve SDB in all individuals,[20–22] leading to the search for alternative strategies such as AMPAkines.[23,24] Clearly, prospective studies are needed to optimally individualize treatment and to examine the causal effect of SDB better in this population.

Substantial efforts toward opioid reduction have been made by public health officials, professional societies, and individual physicians, with mixed results.[25] Regardless, the opioid epidemic is not likely to go away anytime soon. We applaud the authors for highlighting the potential importance of SDB among opioid users. Although the opioid crisis has generated a lot of questions and finger-pointing regarding blame, very few people are asking why these patients die or if treating SDB could prevent opioid-induced complications.

CITATION

Orr JE, Wallace MS, Malhotra A. Might chronic opioid use impact sleep-disordered breathing and vice versa? *J Clin Sleep Med*. 2020;16(6):843–845.

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