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COMMENTARY

Still just the tip of the iceberg

Commentary on 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(5):455–461. doi:10.5664/jcsm.26908

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In 2007, Walker and colleagues[1] published a retrospective case series in the *Journal of Clinical Sleep Medicine* that established chronic opioid use as a risk factor for central sleep apnea (CSA) and ataxic breathing. At that time, they made several very prescient observations. First, that chronic opioid use was rising, fast, especially among those using opioids for non–malignancy-related pain. That is, increasing numbers of patients would be on opioids for conceivably a very long time. Second, that while many believed that the respiratory effects (or indeed, most side effects) of opioids would be minor or transient, their findings suggested that respiratory changes at least are long lasting. Third, that CSA due to narcotics was different from Cheyne-Stokes respiration classically seen in heart failure, but resembled Biot's breathing, for which they proposed potential mechanisms. Finally, they suggested the need to better understand the impact of sleep-disordered breathing on patients taking prescription opioids.

At the time of their study, the authors cited trends in opioid use published in the early 2000s.[2] Yet, opioid prescriptions subsequently continued to rise and would not peak for another 5 years.[3] Thus, the publication, somewhat surprisingly in a sleep journal and describing esoteric respiratory abnormalities, was just the tip of the iceberg for what would become known as the "opioid epidemic," which continues today. Who would have imagined that the epidemic would become so widespread that in a Veterans Administration cohort—typically older men with multiple comorbidities—that opioids would be a more common cause of CSA then heart failure.[4] Of greater concern were subsequent reports that the use of prescription opioids was associated with increased mortality.[5] The authors of that report hypothesized one cause to be changes in respiration in general and sleep-disordered breathing specifically based, in part, on the work by Walker and colleagues.

Since its publication there has been some progress in terms of mechanisms by which opioids lead to CSA (*o*-CSA). Opioids alter the normal respiratory rhythm generation, likely at the level of the pre-Bötzinger complex where neurons express μ-opioid receptors, the activation of which attenuates their action potentials to subthreshold levels.[6] Chronic opioid use is associated with a reduction in the hypercapnic ventilatory response and increase in the hypoxic ventilatory response.[7] Together, these changes explain commonly observed hypercapnia and hypoxemia (which themselves can further promote instability most evident during sleep).[8] Only a little work has been done to better quantify and describe such breathing patterns, beyond the label of "ataxic," and differentiating patterns from more classic Cheyne-Stokes respiration.[9] Thus, more subtle abnormalities that occur with lower doses of opioids might be missed. In terms of treatment, reduction in opioid dose or abstinence has clearly been associated with resolution of *o*-CSA, however difficult this may be to achieve in practice.[10] Continuous positive airway pressure, bilevel positive airway pressure, and adaptive servoventilation show variable efficacy, but improved adaptive servoventilation algorithms may show better control.[11]

However, major questions still remain. Is *o*-CSA important and clinically relevant? There are few data analogous to the morbidity and mortality associated with obstructive sleep apnea or even Cheyne-Stokes respiration. Indeed, some have questioned whether opioid-induced sleep apnea is a real problem.[12] For example, the presence and severity of *o*-CSA or changes in sleep architecture from opioids do not clearly relate to daytime sleepiness or function.[8,13] Psychomotor vigilance testing is impaired, but whether this is a direct effect of opioids or mediated via changes in sleep and breathing is unclear.[8] It seems intuitive that reducing the apnea-hypopnea index should make patients healthier and feel better, yet there are no studies that convincingly suggest that this is so. Thus, although *o*-CSA remains a common problem, and we have a better understanding of its pathogenesis and have better devices to treat it, we still are just exploring the tip of the iceberg of *o*-CSA with respect to patient outcomes. Future notable studies in the journal on this topic will be those that focus on symptoms, quality of life, and health outcomes with long-term treatment.

CITATION

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