The Epidemic of Opioid Use: Implications for the Sleep Physician

Commentary on Javaheri et al. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. *J Clin Sleep Med* 2014;10:637-643.

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The use of opioids has dramatically escalated in the past two decades. According to the 2010 National Survey on Drug Use and Health (NSDUH) survey, an estimated 5.1 million Americans have used some form of prescription pain relief with narcotic analgesics exceeding 238 million prescriptions per annum. Recent reports show that hydrocodone has become the number one prescribed medication in America.¹ The increasing use of opioids has been attributed to several factors including the release of the joint statement on treatment of chronic pain by the American Academy of Pain Medicine and the American Pain Society in 1997 indicating that "pain is often managed inadequately, despite the ready availability of safe and effective treatments" and which downplayed the risk of adverse respiratory effects of long term opioid use.² Other factors contributing to the dramatic increase in use of opioids are liberalization of laws governing the prescription of opioids and the increased marketing by the pharmaceutical industry. Despite the epidemic, there is little scientific evidence that the use of opioids effectively controls non-cancer type pain. In fact, there has been a proportionate increase in physiologic adverse effects from opioid use, including opioid hyperalgesia, misuse and abuse, and a steady increase in opioid-related fatalities.¹ Opioid analgesics are now responsible for more fatalities than the number of deaths from both suicide and motor vehicle accidents, or deaths from cocaine and heroin combined. Drug overdose deaths have increased over 100% between 1999 and 2009. In 2008, opioids contributed to one death every 36 minutes in the United States.¹

The dramatic increase in use of opioids is of concern to sleep specialists. Recent studies have shown that 75 to 85 percent of patients on opioids have at least mild sleep apnea, and 36 to 41 percent have severe sleep apnea, of which the severity is dose dependent.^{3,4} The mechanisms by which opioids cause sleep disordered breathing are poorly understood. Opioids likely act as a respiratory depressant in the central nervous system but also have more complicated effects. One study demonstrated that the use of opioids was associated with both a reduction of the central hypercapnic ventilatory response, and a paradoxical increase in the peripheral hypoxic ventilatory response, which may result in increased loop gain.⁵ In addition to the known cardiovascular and cerebrovascular co-morbidities related to untreated sleep apnea, emerging literature suggests that sleep fragmentation can actually worsen pain syndromes.

This emphasizes the need to address the opioid epidemic crisis head on.

Opioid induced sleep apnea falls within the spectrum of complex sleep apnea, characterized by a combination of obstructive apneas and central sleep disordered breathing. The respiratory pattern may be periodic or non-periodic. The periodic form may be similar to other forms of central apneas or Cheyne-Stokes respiration but typically has a shorter cycle length. The non-periodic form is markedly irregular in amplitude and rhythm. Farney, et al.⁶ described ataxic breathing, central apneas, and sustained hypoxemia in patients receiving long-term opioid medications. The ataxic breathing pattern resembled "Biot's" respirations, commonly seen in patients with severe brain injury with marked variation in the amplitude and the frequency of breaths. The clinical significance and best treatment of complex sleep apnea syndromes, and specifically opioid associated sleep apnea, has been the subject of considerable debate. One form of complex sleep apnea, observed primarily as CPAP-emergent central apnea, has been shown to be a transient phenomenon in the majority of patients, that will generally resolve after 2 to 4 weeks of CPAP therapy.⁷ Despite this experience, efforts to treat opioid associated complex sleep apnea with continuous positive airway pressure (CPAP) have generally been unsuccessful. In 2008, two contradictory studies were published regarding the use of adaptive servoventilation (ASV) mode of PAP. Farney et al.⁸ showed that neither CPAP nor ASV was completely successful in treating ataxic opioid associated sleep disordered breathing. In contrast, Javaheri et al.⁹ described five patients with chronic opioid use, who did not improve with CPAP therapy, but had dramatic improvements with ASV. In more recent study, Ramar et al.¹⁰ found ASV successful in the treatment of opioid-associated sleep apnea in 60% of patients, and their success rate was no different compared with patients with central sleep apnea and heart failure. The reason why ASV was not successful in the remaining patients remains an unanswered question. After these studies, many questions about the clinical manifestations and treatment remained. For example, it was unknown if opioid associated sleep apnea would attenuate with several weeks of CPAP, or if patients would remain adherent to CPAP or ASV over longer periods of time.

With the epidemic of opioid use, sleep physicians can expect to see more of these patients, emphasizing the need for best

treatment practices and guidelines. The study in this issue of *Journal of Clinical Sleep Medicine* by Javaheri et al.¹¹ is a particularly valuable study. Although a retrospective study, the subjects were treated in a consistent manner, the majority of whom had initial CPAP titration studies and then followup studies 4-8 weeks later showing CPAP was ineffective in all. ASV was shown to be effective in the majority, and long term followup showed adherence to therapy, a marker that they were benefitting from the therapy. The data downloaded from the ASV machines at followup showed persistent resolution of sleep disordered breathing. The important points of this study are 1) that fixed CPAP is not effective even after 4-8 weeks, suggesting that opioid associated sleep apnea is a different entity than CPAP-emergent central sleep apnea, 2) ASV is effective in the majority of patients, and 3) that long term adherence to ASV is quite good. Further studies on the effects of CPAP in this entity are not likely to be useful, and clinicians should not feel obligated to use CPAP as initial therapy in these patients, but can proceed to ASV as the treatment most likely to be successful. The current study adds solid information to our knowledge of this entity, but points out further needs for research. Prospective data on a larger number of patients are needed to demonstrate the risk factors for developing CSA while taking opioids, clinical manifestations of this syndrome, the effects of taking other psychoactive drugs, and the long term outcomes of ASV therapy. Dr. Javaheri has made many significant contributions to the field of sleep medicine and to our understanding of central sleep apnea, and is to be congratulated for another excellent study.

CITATION

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