Effect of Opioids on Sleep and Breathing in Chronic Pain Patients

Commentary on Rose et al. Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. *J Clin Sleep Med* 2014;10:847-852.

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Chronic pain is debilitating and distressing to patients and chronic pain clinics have developed to treat these unfortunate patients. The use of opiates to control pain is common. As the management of chronic pain has evolved, the use of opioid medications to treat chronic pain has increased exponentially around the world. In the United States, retail sales of opioid medications increased by 149% from 1997 to 2007.¹ With the increasing use of opioid medications, we have seen an increase in opioid related morbidity and mortality.¹

The link between opioid use and sleep apnea is well established² and has been demonstrated in addiction patients treated with methadone³ and chronic pain patients treated with various opioids.^{4,5}

In this issue of the *Journal of Clinical Sleep Medicine*, Rose et al. report the findings of an observational prospective/retrospective hybrid study.⁶ They prospectively recruited 24 chronic pain patients to undergo diagnostic polysomnogram, psychomotor vigilance testing (PVT), and awake daytime arterial blood gases (ABG). They used a retrospective sample of age, gender, and body mass index (BMI) matched patients from a sleep medicine clinic to determine any differences in severity and type of sleep disordered breathing between opiate treated patients and sleep clinic patients. They used a separate retrospective cohort of 20 healthy controls to compare PVT results. The healthy cohort was noted to have a significantly lower mean BMI than both the sleep and pain clinic patients.

The authors found that 46% of the opioid users had severe sleep apnea defined as an AHI ≥ 30 /h and 71% had moderate sleep apnea (defined as an AHI ≥ 15 /h). This is similar to a retrospective study performed in the US where 36% of patients had an AHI ≥ 30 /hr and 50% had an AHI ≥ 15 /h.⁴ The US study was larger (140 patients) but suffered from possible selection bias. Both studies concluded that patients on opiates for chronic pain have a high incidence of significant sleep apnea. Indeed in the present study, the AHI in the chronic pain patients was similar to age, gender and BMI matched patients attending a sleep clinic and thus felt to be at high risk for sleep apnea. However, the BMI in the opioid treated patients was quite high (mean 34.9) and this would obviously increase the likelihood for developing sleep apnea. Using stepwise linear regression both the BMI and the morphine equivalent dose were significant

predictors of AHI indicating that opioids were having an effect on the severity of sleep apnea.

In this study, 4/24 (17%) had a central apnea index ≥ 5 /h. This is lower than that observed in a group of patients on chronic methadone therapy for substance abuse (30%) or that observed in the US study (33%).^{3,4} The BMI was much higher in the present study, compared to the methadone maintenance study (27) and the US study (29.7) and this may account for the differences in proportions of obstructive and central sleep apnea between studies.

It has been previously suggested that patients on stable doses of opioid medications do not tend to show significant levels of impairment in psychomotor testing.^{7,8} The authors of this study did find that opiate patients had slower reaction times and more frequent lapses when compared to healthy controls; however, a significant amount of data was unavailable for the final analysis. Many of these subjects had sleep apnea which can clearly affect psychomotor vigilance. Many were also on other centrally acting agents, such as benzodiazepines, pregabalin, muscle relaxants, and antidepressants that could also affect psychomotor functioning. Chronic pain itself can impair sleep leading to sleep deficit as well as impaired concentration so pain itself may be contributing to this finding. Thus, the contribution of opioids to this finding is difficult to ascertain. Finally, the significance of changes in psychomotor testing as a predictor of driving accidents is not well established. Studies examining motor vehicle accidents in patients on chronic methadone therapy have generally not found an increase in such patients.⁸ Nevertheless, the findings in the present study are provocative and require further study. In the future, the role of opioids could be assessed by comparing psychomotor vigilance in chronic pain patients on opioids compared with matched patients whose pain is controlled by other means. In addition, studies addressing driving by simulation and by assessing the incidence of motor vehicle accidents in this patient population may provide more direct information on risk.

Perhaps the most interesting finding in this study is the number of opioid patients with chronic hypercapnia. Though the mean PaCO₂ was noted to be within the normal range, 9 out of 20 patients were reported to have hypercapnia (defined as a PaCO₂ ≥ 45 mm hg) on daytime ABGs. However, only 2

patients had more pronounced hypercapnia ($p\text{CO}_2 \geq 50$ mm hg). In a prior study, hypoxemia was noted during quiet wakefulness in patients on opioids for chronic pain with and without sleep apnea.⁵ Hypoxemia in these patients may also have been a manifestation of hypoventilation during wakefulness. Thus, hypoventilation in patients on chronic opioids for chronic pain may be more common than previously thought although the 45% prevalence in this study seems awfully high. This is an area that can easily be pursued in future studies.

Finally, what is the significance of these findings? Sleep apnea is common in this patient population but what are its consequences? In this small cohort of patients, patients with and without sleep apnea had similar Epworth sleepiness scale scores although this is not the best metric to describe sleepiness in individual patients. Sleep apnea was associated with less arousals in opioid patients and thus may result in less sleepiness. However, most patients with and without sleep apnea were sleepy (mean Epworth score was 12-13) and this likely reflects the sedating properties of opioids and the other centrally active medicines the subjects were on.

Sleep apnea both obstructive and central can be treated in patients on opioids. Will such patients derive the same benefits as patients not on opioids? Compliance with positive pressure therapy was quite low in one study of such patients.⁹ Will treatment also lead to improvement in psychomotor vigilance? What if any affect will it have on daytime hypoventilation?

The authors are to be commended for performing the first prospective study in an important but difficult to study group of patients. Like most good studies, it generates more questions than answers.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.