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Sleep-Disordered Breathing in Patients with Opioid Use Disorders In Long-Term Maintenance on Buprenorphine-Naloxone: A Case Series

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Abstract

Background—Rates of opioid overdose deaths are increasing in the United States, leading to intensified efforts to provide medication-assisted treatments for opioid use disorders. It is not clear what effect opioid agonist treatments (i.e., the mu-opioid receptor full agonist methadone and the partial agonist buprenorphine) may have on respiratory function. However, sleep-disordered breathing has been documented in methadone maintenance pharmacotherapy, and there is emerging evidence for similar sleep-disordered breathing in buprenorphine and buprenorphine-naloxone maintenance treatment.

Objectives—Provide further clinical evidence of sleep-disordered breathing emerging in the context of buprenorphine-naloxone maintenance pharmacotherapy.

Methods—We report two additional cases of sleep-disordered breathing that developed in patients with severe opioid use disorders treated successfully as outpatients with buprenorphine-naloxone maintenance. Both patients provided written consent for their clinical information to be included in this case report, and elements of their identities have been masked to provide confidentiality.

Results—Two adult female patients who were stable in buprenorphine-naloxone maintenance treatment developed daytime sleepiness, were referred for evaluation and found to have sleep-disordered breathing. One patient's daytime sleepiness improved with reduction in both buprenorphine-naloxone and other sedating medications as well as initiation of a constant positive airway pressure device (CPAP). The other patient, however, could not tolerate decreases in buprenorphine-naloxone and/or CPAP initiation and her daytime sleepiness persisted.

Conclusion—Buprenorphine-naloxone maintenance treatment can be associated with sleep-disordered breathing. It can be difficult to differentiate the cause(s) of sleep-disordered breathing amongst the effects of buprenorphine-naloxone treatment itself, co-occurring conditions such as obesity and cigarette smoking or other medications, or some combination thereof. Regardless of etiology, sleep-disordered breathing and its consequences present unique challenges to the patient

in recovery from an opioid use disorder, and therefore warrants careful evaluation and management.

Keywords

opioid dependence; sleep-disordered breathing; buprenorphine; buprenorphine-naloxone; sleep apnea

In the United States, annual overdose deaths involving opioid medications have more than tripled since 1999 (4,030 to 15,597),(1) prompting increased efforts to provide medication-assisted treatment of opioid use disorders (OUD). While opioid-induced respiratory depression in overdose situations is well-documented and described,(2, 3) it is not as clear what effects opioid agonist treatments for OUD (i.e., the mu-opioid receptor full agonist methadone and the partial agonist buprenorphine) may have on respiratory function. For instance, clinically-significant sleep-disordered breathing (SDB) has been documented in patients on methadone maintenance treatment.(3) Webster et al (2008) described an abnormal apnea-hypopnea index (AHI) in 75% of 140 patients on “around-the-clock” opioid treatments, with a direct correlation between methadone dose and AHI.(4) Please refer to Table 1 for more information on the clinical significance of objective measures used in the assessment of SDB.

Relative to methadone, buprenorphine has a favorable respiratory profile in overdose situations owing to its “ceiling effect,”⁵ but recently Farney et al (2012) examined patients within 48 hours of buprenorphine induction (n= 70) and reported mild SDB in 63%, and severe apnea in 17% of participants.(6) In buprenorphine *maintenance* treatment, however, there is only one case of central sleep apnea reported: a 30 year-old man with body mass index (BMI) of 28.6 kg/m² taking buprenorphine-naloxone (B/N) 2mg/0.5mg daily. A predominantly central sleep apnea pathology is described in this patient with an AHI of 38.7.(7)

In this paper, we report two additional cases of SDB that developed in patients having severe OUD with physiologic dependence and treated successfully as outpatients on B/N maintenance.

Both patients provided written consent for their clinical information to be included in this case report, and elements of their identities have been masked to provide confidentiality.

Case 1

Ms. A is a 31-year-old woman with a 10-year history of OUD that began with prescription opioid analgesic misuse for post-operative pain following breast reconstruction surgery. She later became an injection heroin user and entered B/N maintenance treatment at a dose of 24mg daily with weekly clinical monitoring, group therapy for relapse prevention and recovery, and supervised urine toxicology in an outpatient clinic setting that provides integrated treatment of OUD and co-occurring psychiatric illness. She rapidly achieved full abstinence and tolerated B/N without adverse events.

At 3 months, she reported progressively worsening daytime sleepiness (including multiple episodes of falling asleep while driving) with snoring and apneic episodes described by her family. Moreover, she reported significant urges and cravings to relapse in relation to the stress that her sleepiness was causing. Observed urine samples confirmed opioid abstinence, adherence with B/N, and abstinence from all substances of abuse including sedative-hypnotics, which in conjunction with B/N have been shown to increase the risk of respiratory depression.⁽⁸⁾ She was referred for a sleep study to rule out SDB.

Her medical history was significant for obesity, gastroesophageal reflux disease, breast reconstruction surgery, migraine headaches, and acne. She also carried psychiatric diagnoses of major depressive disorder and social anxiety disorder which were in partial remission at the time her daytime sedation symptoms began. In addition to B/N, her medications at the time of referral for sleep study included duloxetine 60mg daily for depression, gabapentin 800mg 4 times per day for anxiety, topiramate 200mg daily and sumatriptan 100mg daily as needed for migraine headaches, and, for her acne, she took minocycline 100mg at bedtime. She drank three cups of regular coffee every morning and denied alcohol use. She smoked approximately 2 packs of tobacco cigarettes daily. Her BMI was 33.3, representing a 50-pound weight increase since initiation of B/N.

A sleep study revealed marked obstructive sleep apnea (total AHI of 81.0, average oxygen saturation of 93.0%, lowest saturation 83.0%) and a trial of a constant positive airway pressure device (CPAP) was recommended. Her B/N dose was decreased to 16mg just prior to the sleep study, and remained at that level after the study without reports of increased cravings or withdrawal symptoms. Modafinil 200mg every morning was added to her medication regimen. Other potentially-sedating medications were trimmed: gabapentin was tapered down to 400mg three times per day. She used the CPAP device inconsistently, citing ineffectiveness in improving her sleep; and despite initial improvement, her daytime sleepiness again progressively worsened. Attempts to further decrease B/N dose were unsuccessful owing to increased cravings and risk for relapse to illicit opioid use. Her BMI remained 33.3 and she continues to smoke 2 packs of cigarettes daily, in spite of clinical efforts to support weight reduction and smoking cessation. She remains stably symptomatic, but abstinent of all illicit substances of abuse and adherent to treatment at 3 years B/N maintenance.

Case 2

Ms. B is a 58-year-old woman who had been on B/N maintenance treatment for OUD for 4 years at a dose of 12mg daily. She was monitored weekly in an outpatient clinic and began complaining of progressively worsening daytime sleepiness, without noted snoring or observed apneic episodes or restless legs. She had a history of hepatitis C, and had undergone successful interferon treatment 10 years prior. OUD began after exposure to opioids for pain related to interferon treatment of HCV. She also carried diagnoses of major depressive disorder, obesity, and hyperlipidemia. In addition to B/N, her medications at the time of referral for a sleep study were duloxetine 60mg twice daily and lithium 900mg at bedtime for depression,¹ trazodone 300mg at bedtime for insomnia, and simvastatin 80mg daily for hyperlipidemia. Her BMI was 38.8. She drank two cups of regular coffee every

morning and she denied alcohol and tobacco use. She was referred for a sleep study that revealed a mixed picture of both severe central and obstructive sleep apneas (AHI: 20.2, average oxygen saturation of 93.0%, lowest saturation 81.0%).

B/N was decreased to 8mg without increases in urges or cravings, and she was fitted for a CPAP device that she used consistently. Her daytime sleepiness improved rapidly following these interventions, without significant change in her BMI. She recently underwent successful bariatric surgery and remains clinically stable and abstinent from all substances.

These cases describe the development of SDB in two patients on maintenance treatment for OUD with B/N, which adds to the existing literature describing similar SDB in patients in the induction phase of treatment. Many factors can contribute to SDB, and it is important to note that our two cases do not provide enough data to draw a causal relationship between B/N and the SDB. In particular, both of our patients were on multiple medications that could have impacted daytime wakefulness several of which were concurrently decreased as B/N dose was decreased.

Moreover, both of our patients were overweight at the time of symptom emergence, which is a known risk factor for SDB.⁽⁹⁾ It is notable that in both patients BMI did not change during evaluation and treatment of their SDB, yet Ms. B reported almost complete resolution of symptoms while Ms. A did not. In the case of Ms. A, initiation of B/N coincided with a 50-pound weight gain, which persisted throughout treatment. Therefore, it is possible that her SDB could have been secondary to her weight gain (partially, or in total); a gain that may have been facilitated by the sobriety she achieved through B/N treatment. Ms. B's daytime sleepiness improved, however, with a combination of CPAP and B/N dose reduction without change in BMI. Tobacco cigarettes are another potential risk factor for SDB,⁽¹⁰⁾ so Ms. A's SDB and daytime sleepiness may have been partly maintained or aggravated by her smoking habit.

Given the established and emerging data on the relationship between opioid agonist and partial agonist medications and the respiratory drive system, it is reasonable to consider buprenorphine or B/N as at least a contributory factor in these patients' SDB, or (as in the case of Ms. A) as a secondary consequence of life changes associated with sobriety achieved with B/N treatment. Therefore, prescribers should be alert to the possible emergence of daytime sleepiness as a result of SDB in patients being treated with B/N.

Regardless of the etiology or treatment success being uni- or multi-factorial in nature, the emergence of marked daytime sleepiness in patients on B/N maintenance treatment presents unique management challenges. The distress described by our patients represented a significant challenge to their ongoing sobriety and recovery. Recognizing that a relationship may exist between B/N maintenance treatment and clinically-significant SDB encourages clinicians to incorporate questions about sleep quality into their routine discussions with

¹The Food and Drug Administration has not approved the use of lithium as an augmentation medication strategy for the treatment of unipolar depression. Nonetheless, evidence supports lithium's efficacy as an adjunctive medication for this condition. See: Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2007;68(6):935.

patients and their families. The Epworth Sleepiness Scale, for example, is an 8-question, validated screen for assessing daytime sleepiness that can be easily delivered in the clinic setting and may be helpful in establishing and tracking daytime sleepiness severity.(11) However, further history about sleepiness and sleep patterns (also from sleep partners), laboratory studies, physical examination, and a comprehensive medication review may also be needed to adequately assess the problem.(12)

Clinicians should also be alert to the possibility that, once recognized, with referral for appropriate evaluation and treatment this condition may be reversible through a combination of medication adjustments and/or mechanical or behavioral interventions tailored to the patients' individual needs (as was the case with Ms. B). Unfortunately, interventions to address Ms. A's SDB were unsuccessful in mitigating her daytime sleepiness. Nonetheless, Ms. A remained abstinent despite her SDB and its consequences, and we can speculate on the positive role that empathically and systematically exploring her symptoms and concerns regarding her SDB have played in her continued abstinence. Our cases highlight that the consequences of SDB can result in significant impairment in daily functioning and can leave patients more susceptible to exacerbations of other psychiatric or medical illnesses as well as more vulnerable to substance relapse. Therefore, recognizing and treating SDB in patients on B/N maintenance treatment may have a positive effect on overall treatment.

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Table 1**Sleep Studies and Sleep-Disordered Breathing**

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- During sleep studies, sleep-disordered breathing (SDB) is quantified by measuring the number of:
 - apneic (cessation of airflow 10 seconds) episodes during an observed sleep session.
- AND
- hypopneic (30% reduction in airflow lasting 10 seconds associated with 4% decline in oxygen saturation) episodes during an observed sleep session.
 - The total number of apneic and hypopneic episodes per hour of sleep, or **apnea-hypopnea index (AHI)**, is an important measure of the quality of breathing during sleep.
 - Clinicians make the distinction between central versus obstructive apneic or hypopneic episode by correlating the SDB episodes with data from other physiologic monitors, such as: electroencephalogram, electrocardiogram, pulse oximetry, body position monitor, inductive plethysmography, and nasal pressure transducer.
 - Treatments for SDB can include use of continuous positive airway pressure devices (CPAP), supplemental oxygen, custom-made oral appliances, and upper airway surgery.
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