

# Hypoxemia in patients on chronic opiate therapy with and without sleep apnea

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## Abstract

**Objective** Animal models have shown a quantal slowing of respiratory pattern when exposed to opioid agonist, in a pattern similar to that observed in central sleep apnea. We postulated that opioid-induced hypoventilation is more likely to be associated with sleep apnea rather than hypoventilation alone. Since we did not have a direct measure of hypoventilation we used hypoxemia as an indirect measure reasoning that significant hypoventilation would not occur in the absence of hypoxemia.

**Methods** We conducted a retrospective analysis of 98 consecutive patients on chronic opioid medications who were referred for overnight polysomnography. All patients

on chronic opioids seen in the chronic pain clinic were referred for a sleep study regardless of whether they had sleep symptoms or not. Sleep-related hypoxemia was defined as arterial oxyhemoglobin saturation of less than 90% for more than 5 min with a nadir of  $\leq 85\%$ , or greater than 30% of total sleep time at an oxyhemoglobin saturation of less than 90%.

**Results** Of the 98 patients, 36% (95% CI 26–46%) had obstructive sleep apnea, 24% (95% CI 16–33%) had central sleep apnea, 21% (95% CI 14–31%) had combined obstructive and central sleep apnea, in 4% (95% CI 0–10%) sleep apnea was classified as indeterminate, and 15% (95% CI 9–24%) had no sleep apnea. Opioids were potentially responsible for hypoxemia during wakefulness in 10% of patients (95% CI 5–18%) and for hypoxemia during sleep not clearly associated with apneas/hypopneas in 8% of patients (95% CI 4–15%). Two patients (2%, 95% CI 0–7%) had sleep-related hypoxemia in the absence of sleep apnea or hypoxemia during wakefulness.

**Conclusions** Patients on chronic opiate therapy for chronic pain have an extremely high prevalence of sleep apnea and nocturnal hypoxemia. Hypoxemia can occur during quiet wakefulness in patients on chronic opioid medications with and without sleep apnea. In patients on chronic opioid therapy, isolated nocturnal hypoxemia without coexisting sleep apnea or daytime hypoxemia is very uncommon.

**Keywords** Sleep apnea · Hypoxemia · Hypoventilation · Opioids

## Introduction

It is well established that opioids can cause central sleep apnea [1]. In a recent study, we showed that patients

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receiving opioids for chronic pain have a high prevalence of central, obstructive, and combined obstructive and central sleep apnea [2]. Similarly, Wang et al. [3] found that 30% of patients on methadone maintenance therapy had central sleep apnea. In addition, opioids result in altered responses to hypoxic and hypercapnic stimuli with a reduced ventilatory response to hypercapnia and a variable response to hypoxia depending on whether the ingestion of opioids is acute or chronic [3–6].

Opioids have various effects on respiration in mammals. These effects include reduction in tidal volume, gas exchange, and respiratory rate, leading eventually to respiratory arrest at high doses [7–9]. Experimental studies have shown that opioid-induced disruption of respiratory rhythm is mediated by generalized suppression of respiratory network activity [7, 10]. This observation is further validated by a number of studies that have shown that endogenous opioids and  $\mu$  subtypes of opioid receptors are found in respiratory centers in the pons and medulla [8, 9, 11–15]. There are two separate brainstem rhythm generators, namely the pre-Botzinger neuronal network and the retrotrapezoid nucleus/parafacial respiratory group [16–19]. The latter contains the pre-inspiratory neurons. Subsequently, it has been shown that the pre-Botzinger neuronal complex is the more dominant of these centers and exhibits opioid receptors [15, 18, 20]. Opioid agonist acting on sliced sections containing only the pre-Botzinger complex neurons resulted in a continuous increase in inspiratory periods resulting in a dose-dependent graded reduction in respiratory rate [12]. This finding was consistent with an experimental study showing that  $\mu$  opioid agonist hyperpolarized a subset of pre-Botzinger complex neurons [11]. However, when the two rhythm generators were taken together in an en bloc preparation of neuronal tissue, opioid agonist resulted in quantal slowing of respiratory rhythm [18, 20]. With quantal slowing, the respiratory rate drops precipitously to an integer multiple of the baseline rate. This pattern of breathing is somewhat similar to what occurs in central sleep apnea syndrome not due to Cheyne–Stokes breathing. If respiratory controllers in adult humans have the same functional structure, we postulate that sleep-related hypoventilation due to opioid medications will usually be associated with sleep apnea, rather than hypoventilation alone without evidence of apneas and/or hypopneas. Similar to most adult sleep laboratories, we do not routinely obtain a measure of ventilation such as end-tidal  $\text{CO}_2$ . Therefore, we used hypoxemia as an indirect marker of potential hypoventilation. We reasoned that significant clinically important hypoventilation was unlikely to occur in the absence of hypoxemia. However, hypoxemia can certainly occur in the absence of hypoventilation.

## Methods

**Subject selection** We conducted a retrospective analysis of 98 consecutive patients seen at the Lifetree Pain Clinic (Salt Lake City, UT), on round-the-clock opioid medications who were referred for overnight polysomnography between July and October 2005. All patients at the Lifetree Pain Clinic on chronic opioids are referred for a sleep study regardless of symptoms as part of their evaluation. The patients were considered to be on round-the-clock opioids if they regularly used short acting opioids four or more times during a 24-h period, were on extended release opioids, or both. We considered long-acting opioids and sustained release opioids to be equivalent for the purpose of this study. All patients were on opioids for at least 6 months with their daily dose stable for at least 4 weeks.

**Polysomnography** All patients underwent nocturnal polysomnography for diagnostic evaluation at MedOne Medical sleep laboratory (Sandy, UT, USA). They underwent standard nocturnal polysomnography with recordings of electroencephalogram, electrooculogram, submental and bilateral leg electromyograms, and electrocardiogram. An oral nasal thermistor and nasal pressure transducer were used for qualitative measure of airflow. Respiratory effort was measured by thoracoabdominal piezoelectric belts. Estimation of arterial oxyhemoglobin saturation was made using a pulse oximeter with the probe placed on the patient's finger. All signals were collected and digitized on a computerized polysomnography system (Rembrandt, AirSep Corp., Buffalo, NY, USA).

The record was analyzed for apneas, hypopneas, electroencephalogram arousals, and oxyhemoglobin desaturations. Apnea was defined as the absence of airflow for at least 10 s. If respiratory effort was present during this apneic episode, it was defined as an obstructive apnea and when respiratory effort was absent it was termed a central apnea. Hypopnea was defined as a visible reduction in airflow lasting at least 10 s and associated with either a 3% drop in arterial oxyhemoglobin saturations or an electroencephalogram arousal. An arousal was defined according to criteria proposed by the Atlas Task Force [21].

Patients were classified as having obstructive sleep apnea if the apnea–hypopnea index was  $\geq 5$  events per hour and the central apnea index was  $< 5$  events per hour and the difference between the apnea–hypopnea index and central apnea index was  $\geq 5$  events per hour. If this difference was  $< 5$  events per hour, the type of sleep apnea was classified as indeterminate. Patients were classified as having central sleep apnea if the central apnea index was  $\geq 5$  events per hour and the obstructive apnea index was  $< 5$  events per hour, and combined central and obstructive sleep apnea if the central

apnea index and the obstructive apnea index were  $\geq 5$  events per hour. The level of severity of sleep apnea was classified as follows: mild, apnea-hypopnea index  $5 < 15$  events per hour; moderate, apnea-hypopnea index  $15 < 30$  events per hour; and severe, apnea-hypopnea index  $\geq 30$  events per hour.

Sleep-related hypoxemia was defined using the two definitions suggested by the American Academy of Sleep Medicine [1]: (1) an arterial oxyhemoglobin saturation ( $\text{SpO}_2$ ) during sleep of less than 90% for more than 5 min with a nadir of  $\leq 85\%$  or (2) greater than 30% of total sleep time at a  $\text{SpO}_2$  of less than 90%. These definitions are somewhat arbitrary and were not originally intended to characterize hypoxemia in patients with sleep apnea. However, definition 1 is relatively liberal and we reasoned that hypoxemia that did not meet this definition might not be clinically significant.

Sleep apnea is expected to cause hypoxemia. We were interested to see if opiates could also induce hypoxemia when sleep apnea was absent. However, there were only 15 patients who did not have sleep apnea. To address whether opiates could induce hypoxemia by mechanisms other than precipitating sleep apnea, we looked at the records of the patients with sleep apnea closely. Specifically, we examined the initial wakefulness period just prior to the start of the sleep study to determine if hypoxemia was present. Hypoxemia present during quiet wakefulness could not be due to sleep apnea since the patients were not asleep. Hypoxemia during quiet wakefulness was defined as a sustained  $\text{SpO}_2$  of less than 88% for at least 5 min at rest on room air prior to the start of the sleep study. The sleep record was reviewed carefully to ensure that periods of wakefulness truly reflected wakefulness rather than a transition from wakefulness to stage 1 sleep. We also examined the entire sleep record in patients with sleep apnea. In some patients with mild to moderate sleep apnea, the presence of sleep apnea was sporadic during the night and there were prolonged periods where the breathing pattern looked relatively regular without evidence of apneic/hypopneic events or a slow irregular breathing pattern. If there were at least 30 consecutive minutes of such breathing, we tried to determine whether hypoxemia occurred during these event-free intervals. Again, we reasoned that this would be another circumstance where opiates induced hypoxemia in the absence of sleep-disordered breathing events.

A detailed questionnaire is completed by the patients before the sleep study which asks the patient to answer yes or no to whether they suffer from a number of coexisting medical conditions. In addition, a list of the patient's medications is provided. This questionnaire was reviewed to check for the presence of any cardiopulmonary or

neurological condition which could potentially cause hypoxemia during wakefulness or sleep. Some patients had a cardiopulmonary disorder that was not considered sufficiently severe to cause hypoxemia by itself. However, we were concerned that this cardiopulmonary disorder might interact with opiate usage and produce hypoxia when opiates by themselves might not have. To take the most conservative approach, we did not include these patients in our estimates of opiate-induced hypoxia. Similarly, for any patient with hypoxemia and a body mass index (BMI) greater than  $35 \text{ kg/m}^2$ , the hypoxemia was attributed to the obesity since hypoxemia may not have occurred if obesity had not been present.

Pearson correlation was performed to see if age, cigarette smoking (cigarettes per day), BMI, apnea/hypopnea index (AHI), and the amount of opioid and benzodiazepine ingested per day correlated with the degree of nocturnal hypoxemia. A multiple regression model was then used to determine if these factors independently explained the variability in hypoxemia. The amount of opioid ingested per day was estimated from the list of opioid medications prescribed to the patient. A number of different opioids were used for chronic pain therapy. They were converted into a morphine equivalent dosage in milligrams per day [2]. Thirty-four patients took concurrent benzodiazepines. Benzodiazepines were converted into a diazepam equivalent dosage in milligrams per day.

The study protocol was approved by the institutional review board of the Western New York Veteran Affairs Healthcare System, Buffalo, New York.

## Results

The median age of the study population was 48 years (range 22–80 years) and the male to female ratio was 1.39 to 1. The range of body mass index was 20.7 to  $47.3 \text{ kg/m}^2$  (median  $30.1 \text{ kg/m}^2$ ). Fifty percent of the potential patient pool failed to show up for their scheduled sleep study.

Of the 98 patients reviewed, 35 (36%, 95% CI 26–46%) had obstructive sleep apnea and 23 (24%, 95% CI 16–33%) had central sleep apnea (Table 1). Twenty-one patients had combined obstructive and central sleep apnea (21%, 95% CI 14–31%). Sleep apnea was classified as indeterminate in four of the patients (4%, 95% CI 1–10%). Fifteen patients (15%, 95% CI 9–24%) out of the 98 patients had no sleep apnea diagnosed on nocturnal polysomnography. We used two different criteria to evaluate for sleep-related hypoxemia as outlined above. Forty-five of the 83 patients with sleep apnea met both the criteria for sleep-related hypoxemia. An additional 18 patients met only the first criteria

**Table 1** Prevalence of hypoxemia based on class and severity of sleep apnea

	Number of patients	Number of patients with hypoxemia	Percent (95% CI)
No sleep apnea	15	9	60 (32–83)
Mild (AHI 5–<15 events per hour)	25	15	60 (39–79)
Moderate (AHI 15–<30 events per hour)	18	15	83 (59–96)
Severe (AHI ≥30 events per hour)	40	33	82.5 (67–93)
Obstructive sleep apnea	35	26	74 (57–88)
Central sleep apnea	23	17	74 (52–90)
Combined sleep apnea	21	18	86 (64–97)
Indeterminate sleep apnea	4	2	50 (7–93)

for sleep-related hypoxemia where they had at least 5 min of SpO<sub>2</sub> below 90% with a nadir ≤85%. There were no patients who met the second criteria alone. Twenty of the patients with sleep apnea did not have sufficient hypoxemia during the night to meet either of our definitions for significant nocturnal hypoxemia.

A flow chart outlining the presence or absence of sleep apnea and hypoxemia during wakefulness and sleep is shown in Fig. 1. Seventeen patients with sleep-related hypoxemia also had hypoxemia during quiet wakefulness (17%, 95% CI 10–26%) of which 11 patients had comorbidities that might have potentially contributed to the hypoxemia (five with BMI >35 kg/m<sup>2</sup>, three with asthma, one with congestive heart failure, one with chronic bronchitis, and one with multiple sclerosis). There were six patients (6% 95% CI 2–13%) who had no identifiable cause to explain their hypoxemia during wakefulness except for the use of opioids. Three of these patients had an irregular breathing pattern during wakefulness. These patients had breathing pauses and an irregular slow breathing pattern during both wakefulness and sleep. The other three patients had a regular breathing pattern during wakefulness but were still hypoxic.

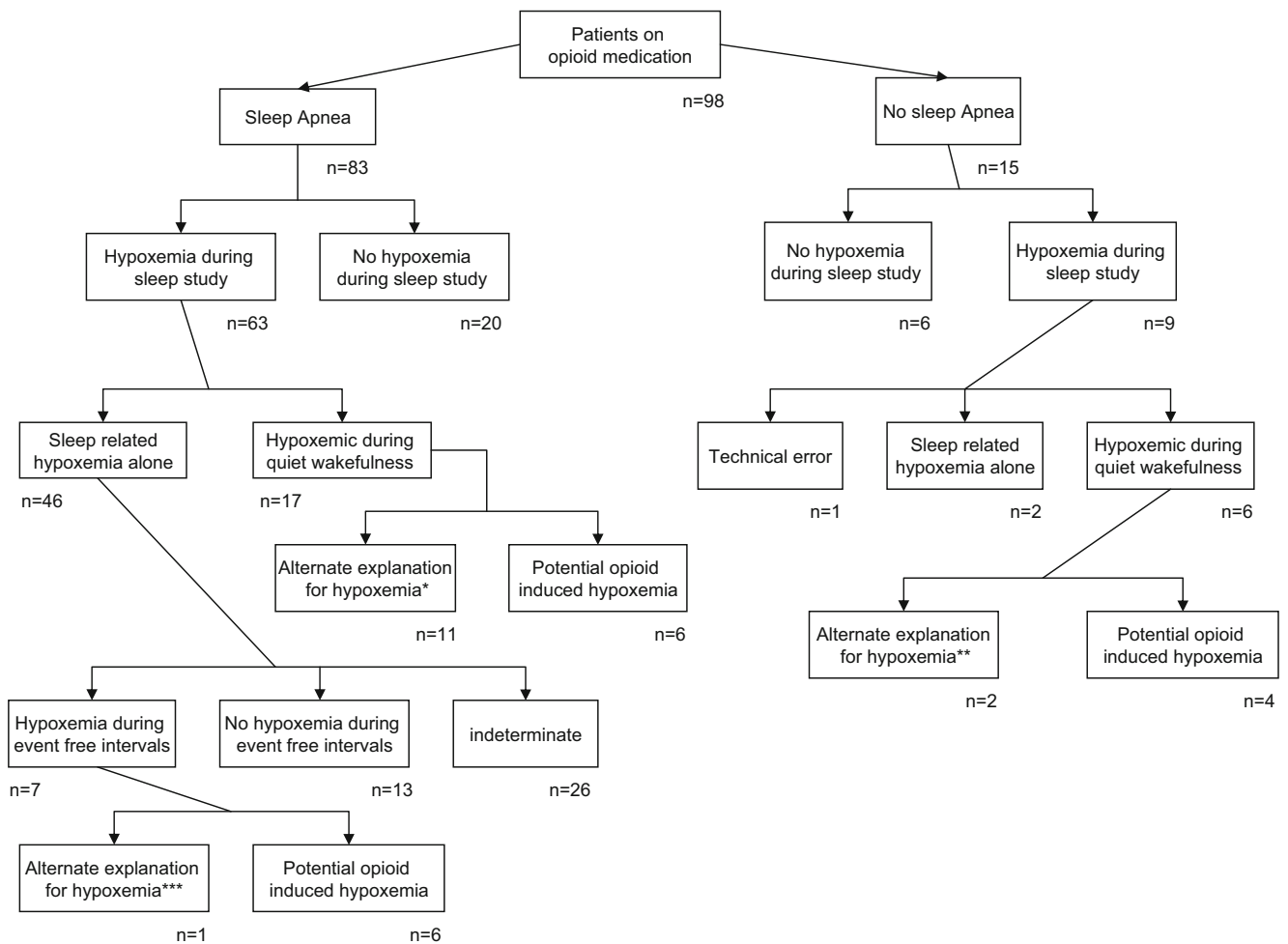
Patients were also classified on the basis of the severity of their sleep apnea. Twenty-five patients had mild sleep apnea (26% 95% CI 17–35%), 18 had moderate sleep apnea (18% 95% CI 11–28%), and 40 patients had severe sleep apnea (41%, 95% CI 31–51%) (Table 1).

We looked at the prevalence of sleep-related hypoxemia based on the class and severity of sleep apnea (Table 1). Of course, hypoxemia in the presence of sleep apnea is likely due to the apneic–hypopneic events. However, we also reviewed the sleep records to see if, during periods when apnea/hypopnea did not occur for at least 30 min, hypoxemia was present. A representative example of a patient with hypoxemia during sleep in the absence of apneas/hypopneas or an irregular breathing pattern is shown in Fig. 2. Of the patients with mild sleep apnea, 11 out of 25 patients had sleep-related hypoxemia without hypoxemia

during wakefulness. On review of their sleep study, it was noted that four out of these 11 patients had sleep-related hypoxemia even during periods free of any apneas/hypopneas but one of these patients had asthma which could have potentially contributed to sleep-related hypoxemia and hence was excluded. The nasal pressure contour and the lack of abdominal–chest wall paradox did not suggest sustained elevated upper airway resistance as a potential cause of the hypoxemia. Amongst the patients with moderate sleep apnea 11 out of 18 patients had sleep-related hypoxemia with normal saturation during wakefulness. Review of their sleep studies showed that three patients had periods of hypoxemia without any concomitant apneas/hypopneas, six patients had normal saturations during event-free periods and two patients did not have sufficient periods of time that were event-free making the evaluation indeterminate. Sleep studies of patients with severe sleep apnea were also reviewed to evaluate for a similar pattern of hypoxemia in the absence of events but these patients did not have sufficient event-free periods and hence this determination could not be made.

Nine out of the 15 patients without sleep apnea had sleep-related hypoxemia, but one of them had an artifact in his pulse oximetry signal and hence was excluded from further review. Six patients out of the remaining eight also had hypoxemia during wakefulness hence leaving two patients with pure sleep-related hypoxemia (2%, 95% CI 0–7%). Out of the six patients with hypoxemia during wakefulness, only two patients had cardiopulmonary conditions (asthma and chronic bronchitis) potentially contributing to their hypoxemia, leaving four patients with only opioids as a potential cause of their hypoxemia during wakefulness. In all of these patients, the breathing pattern was regular without pauses or an irregular slow pattern.

In all, opioids were potentially responsible for sleep-related hypoxemia in eight out of the 98 patients in the absence of sleep apnea or during periods of sleep without any apnea or hypopneas (8%, 95% CI 4–15%). During wakefulness, opioids alone were attributed to be the



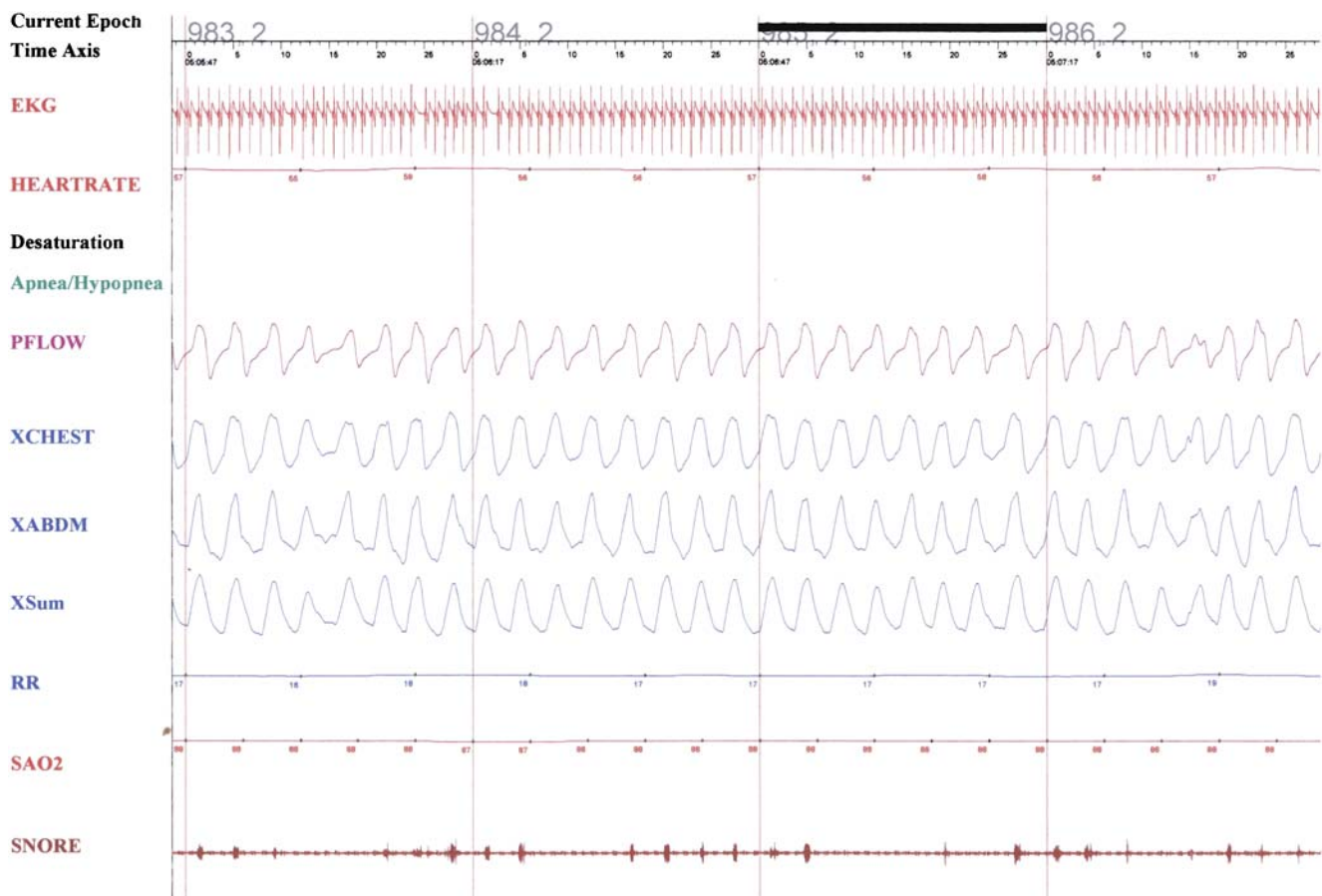
**Fig. 1** Flow chart outlining the presence or absence of sleep apnea and hypoventilation/hypoxemia during sleep and wakefulness amongst the study population. Footnote: \*Alternate causes of hypoxemia: five with BMI >35 kg/m<sup>2</sup>, three with asthma, one with

congestive heart failure, one with chronic bronchitis, and one with multiple sclerosis. \*\*Alternate causes of hypoxemia: one with asthma and one with chronic bronchitis. \*\*\*Alternate cause of hypoxemia: asthma

potential cause of hypoxemia in ten out of 98 patients (10%, 95% CI 5–18%).

The median for the morphine equivalent dose was found to be 180 mg per day (range of 7.5 to 935 mg). Thirty-four patients were also on concomitant benzodiazepines. The median dosage of benzodiazepine as diazepam equivalents in milligrams per day amongst these patients was 20 mg (range 2.5 to 80 mg). A weak but significant correlation was seen between the morphine equivalent dose and percent of total recording time spent at a SpO<sub>2</sub> below 90% ( $r=0.237$ , 95% CI 0.034–0.425%;  $p$ -value 0.023). Similarly, a significant albeit weak correlation was also seen between age and BMI and percent of total recording time spent at a SpO<sub>2</sub> below 90% ( $r=0.225$ , 95% CI 0.021–0.41%,  $p$ -value 0.031 and  $r=0.211$ , 95% CI 0.006–0.39%,  $p$ -value 0.043, respectively). No significant correlation was seen between the AHI and cigarette smoking and percent of total recording time spent at a SpO<sub>2</sub> below 90%. A multiple regression model between

hypoxemia (percentage time spent at a SpO<sub>2</sub> below 90%) and morphine equivalent dose, age, and BMI showed that morphine equivalent dose, age, and BMI all had an independent effect on hypoxemia. Together, these three factors explained 17.5% of the variance in hypoxemia ( $p$ -value 0.0007). No significant correlation was seen between the oxygen saturation nadir during the sleep study and the amount of opioid ingested, AHI, age, and cigarette smoking. The BMI was significantly associated with the oxygen saturation nadir showing that the higher the BMI the lower the oxygen saturation nadir ( $r=0.25$ , 95% CI 0.046–0.43%,  $p$ -value 0.017). No significant correlation was seen between either the oxygen saturation nadir or percent of total recording time spent at a SpO<sub>2</sub> below 90% during the sleep study and the amount of benzodiazepine ingested. State-specific (REM vs. nREM) correlations could not be explored as the percent time spent below 90% saturation was not expressed separately for nREM and REM sleep.



**Fig. 2** Patient with mild sleep apnea demonstrating hypoxemia during a portion of the study where no respiratory events were noted. Notice the absence of an irregular or slow breathing pattern

## Discussion

The increasing prevalence of opioid use in the US and around the world has made opioid-related sleep disorders a significant health concern [22]. While illicit use of opioids is widespread, they are also commonly prescribed for acute or chronic pain, restless leg syndrome, and they are commonly employed during anesthesia [23, 24]. Farney et al. reported ataxic breathing, central apneas, obstructive hypopneas, and prolonged hypoxemia in three patients using chronic opioids [25]. In patients on methadone maintenance therapy, a 30% prevalence of central sleep apnea was observed [3]. Opioids were noted to decrease the hypercapnic ventilatory response but surprisingly an increased hypoxic ventilatory response was observed when compared to controls not taking methadone [3, 5]. In a larger cohort of patients ( $n=140$ ), we reported that patients on round-the-clock opioids had an increased prevalence of obstructive and central sleep apnea. The severity of the sleep disturbances was directly related to the daily dose of methadone in these patients [2]. The results of the present study showed that 85% (95% CI 76–91%) of patients had

an abnormal apnea–hypopnea index, while 15% (95% CI 9–24%) had no sleep apnea. Of those with abnormalities, 36% had obstructive sleep apnea, 24% had central sleep apnea, 21% had both central and obstructive sleep apnea, and 4% had sleep apnea of indeterminate type. These results are consistent with the prevalence of different classes of sleep apnea reported in our recent study [2]. We did not have a control group in this study. Nevertheless, a prevalence of 85% for laboratory evidence of sleep apnea is certainly considerably higher than the usual population estimates obtained from a middle-aged population, 24% for men and 9% for women [26]. In addition, laboratory evidence for central sleep apnea was seen in 45% of our patients. Population estimates for central sleep apnea using a more liberal criteria of a central apnea index  $\geq 2.5/h$  are 1.7% in men aged 45–64 years and 12.1% in men over 65 years of age [27]. One limitation of our study is that, although a sleep study was ordered for every chronic pain patient on opiate therapy, only 50% of patients actually went for their sleep study. Selection bias is quite possible as patients with greater sleep complaints might be more likely to show up for their scheduled sleep study appointment

although other factors such as travel distance, work schedule, and insurance considerations may also have contributed to the no show rate.

A number of important experimental studies in mammals have improved our understanding of the brainstem respiratory centers. There are two distinct respiratory rhythm generators in the medulla (pre-Botzinger neuronal network and the retrotrapezoid nucleus/parafacial respiratory group) [16–19]. These centers are thought to be coupled and result in a normal respiratory rhythm in the resting state [20]. Of interest for this study is the fact that the pre-Botzinger neuronal network exhibits  $\mu$  opioid receptors that when occupied can cause inhibition of their activity [11, 12]. When sliced preparation of the ventral medulla of rodents comprising only the pre-Botzinger neurons are exposed to DAMGA (d-Ala(2),NMePhe(4),Gly-ol(5)enkephalin), a  $\mu$  opioid receptor agonist, there is a continuous increase in the inspiratory period [20]. However, DAMGA caused a step-like precipitous increase in the inspiratory periods in preparations comprising of both the pre-inspiratory neurons and pre-Botzinger neurons [20]. This type of quantal slowing of inspiratory activity is seen also in vivo in vagotomized, anesthetized juvenile rats given mild doses of the opioid agonist fentanyl [28]. In humans, a somewhat similar pattern of rhythm slowing is seen in central sleep apnea related to opioid use.

Breathing is regulated continuously to adapt to exercise, pregnancy, and disease states [20]. While breathing mechanisms are stable and well coordinated during the awake state, they are found to be more labile during sleep. This state dependency was also shown in animal models where targeted ablation of pre-Botzinger complex neurons initially led to respiratory disturbances during sleep and only later with significant neuronal loss, during the awake state [29]. Feldman and Del Negro [20] using this data suggested that the increased incidence of central sleep apnea in patients older than 65 [27], may be a result of cumulative loss of pre-Botzinger complex neurons as a part of aging. Also hypoxia resulting from the central apneas may lead to further neuronal loss forming a vicious cycle [20].

Our results show that hypoxemia during wakefulness is not uncommon in patients on long-term opioid medications. Ten patients (10%, 95% CI 5–18%) out of our study population had awake state hypoxemia which could potentially be attributed to opioids. Of these ten patients, six patients (6%, 95% CI 2–13%) also had sleep apnea and worsening of their hypoxemia during sleep. However, hypoxemia during wakefulness can occur even in the absence of sleep-disordered breathing. A caveat is that this data was obtained during quiet wakefulness with the patient attempting to fall asleep. The sleep records were reviewed closely and epochs that might be considered to display any

evidence of transitioning into stage 1 sleep were excluded. Nevertheless, this situation is clearly different than daytime wakefulness when the patient is actively interacting with their environment, and the presence of hypoxemia during the daytime may be less.

Patients on long-term opioid medications have an increased mortality rate which is rising and for the most part is because of unintentional overdose [30–32]. The reason behind this increase in the number of deaths due to opioid use is not clearly understood. Our data shows that hypoxemia in patients on opiates occurs primarily in association with sleep apnea but can occur when sleep apnea is not occurring under three possible situations. This includes sleep-related hypoxemia in patients with sleep apnea during periods free of any apneas or hypopneas, hypoxemia during sleep in patients without sleep apnea albeit rarely, and hypoxemia during wakefulness. In our study population, 30 out of the 98 patients (31%, 95% CI 22–41%) had hypoxemia under one of the above circumstances. If we include patients who had sleep-related hypoxemia in association with sleep apnea, then 71 out of the 98 patients (72%, 95% CI 64–81%) had hypoxemia potentially related to chronic opioid use on the premise that none had co-morbidities severe enough to cause hypoxemia independently and that opioid use might have significantly contributed to the patients' sleep apnea. We found weak but significant correlations between the amount of opioids ingested daily, age, and BMI and the percentage of total sleep time spent at  $SpO_2 < 90\%$ . Our results showed that the amount of opioid ingested daily independently explained a portion of the variance in the hypoxemia. We may not have found a stronger correlation because we used the prescribed dosage of opioids for our analysis which may differ significantly from the actual dosage ingested by the patient on the day of the overnight polysomnography as patients with chronic pain tend to adjust their day-to-day dosage based on their level of pain. Interestingly, there was no significant correlation between the AHI and the amount of opioid ingested daily. This could indicate that the AHI may not be as good a metric at providing an estimate of the severity of opiate-induced sleep-disordered breathing as it is for routine obstructive sleep apnea. Whether hypoxemia and/or sleep apnea associated with opioid usage can be used as a marker to predict chronic pain patients at higher risk of sudden death needs to be determined in subsequent studies. In fact, we do not yet know when patients on chronic pain therapy die, i.e., whether death is more common at night or during the day.

Thirty-five percent of patients were on coexisting benzodiazepines. It is well appreciated that benzodiazepines can worsen or precipitate obstructive sleep apnea in predisposed individuals [33]. In a prior study, we found that the diazepam equivalent dosage correlated with the

central apnea index in chronic pain patients on chronic opiates indicating that benzodiazepines can have an additive effect [2]. However, in this study, we did not find a significant relationship between diazepam equivalent dosage and our indices of hypoxemia, the percent time spent below 90% and the oxygen saturation nadir.

A limitation of this study is that oxygen saturation only measures hypoxemia and does not provide information regarding the underlying pathophysiological mechanisms. Ideally, we would have liked to have measured an index that monitored the level of partial pressure of carbon dioxide ( $p\text{CO}_2$ ) like end-tidal or transcutaneous  $p\text{CO}_2$ . This procedure is not performed routinely in most adult sleep laboratories including our own. It is unlikely that the use of hypoxemia as a surrogate marker of potential hypoventilation missed clinically significant hypoventilation. However, hypoxemia can be caused by ventilation/perfusion mismatch. Thus, not all the episodes of hypoxemia which we observed may have been due to hypoventilation.

In conclusion, chronic opioid therapy results in a high prevalence of obstructive, central, and combined sleep apnea as shown by our earlier report. Hypoxemia can occur during wakefulness in patients on chronic opioid medications with and without sleep apnea. Long-term opioid use can cause hypoxemia in the absence of apneas or hypopneas in patients with sleep apnea. Finally, in support of our hypothesis, isolated nocturnal hypoxemia without coexisting sleep apnea or daytime hypoxemia is very uncommon.

*Potential clinical significance* Patients on chronic opiate therapy for chronic pain have an extremely high prevalence of sleep apnea and nocturnal hypoxemia. Clinicians should have a high index of suspicion for sleep-disordered breathing in this patient population. Whether the presence of sleep apnea, particularly central sleep apnea, has the same implications in patients on opiate therapy as it does in the general population remains to be determined.

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