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TITLE PAGE:

TITLE: Sleep disordered breathing (SDB) in patients receiving therapy with buprenorphine/naloxone.

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ABSTRACT:

Background: Patients using chronic opioids are at risk for exceptionally complex and potentially lethal disorders of breathing during sleep including central and obstructive apneas, hypopneas, ataxic breathing and non-apneic hypoxemia. Buprenorphine, a partial μ-opioid agonist with limited respiratory toxicity, is widely used for treatment of opioid dependency and chronic non-malignant pain however its potential for causing sleep disordered breathing has not been studied.

Methods: 70 consecutive patients admitted for therapy with buprenorphine/naloxone were routinely evaluated with sleep medicine consultation and attended polysomnography.

Results: The majority of patients were young (mean age ± SD = 31.8 ± 12.3 years), non-obese (mean BMI ± SD = 24.9 ± 5.9 kg/m^2) and female (60%). Based upon the apnea/hypopnea index (AHI), at least mild sleep disordered breathing (AHI ≥ 5/hr) was present in 63% of the group. Moderate (AHI ≥15 to < 30/hr) and severe sleep apnea (AHI ≥ 30/hr) was present in 16% and 17% respectively. Hypoxemia, defined as an SpO2 of < 90% for ≥ 10% of sleep time, was present in 27 patients (38.6%)

Conclusions: Despite the putative protective ceiling effect regarding ventilatory suppression observed during wakefulness, buprenorphine may induce significant alterations of breathing during sleep using routine therapeutic doses.

KEY WORDS:

Opioids
Buprenorphine/Naloxone
Central sleep apnea
Biot's respiration/Ataxic breathing
Polysomnography
Random Forest

ABBREVIATIONS:

SDB	Sleep Disordered Breathing
AHI	Apnea plus Hypopnea Index
OAI	Obstructive Apnea Index
CAI	Central Apnea Index
HI	Hypopnea Index
BMI	Body Mass Index
OSA	Obstructive Sleep Apnea
PSG	Polysomnography

INTRODUCTION: Patients using chronic opioids are at risk for exceptionally complex and potentially lethal disorders of breathing during sleep including central and obstructive apneas, hypopneas, ataxic breathing and non-apneic hypoxemia [1-5]. The mortality rates associated with the use of non-illicit opioids have increased in parallel with the unprecedented escalation of opioid prescriptions since 1997 [6-9].

Buprenorphine is a semisynthetic opioid partial μ-agonist that has become widely used for therapy of opioid dependency since it was patented in 1969 and was approved for marketing in the United States in 1981. The retail distribution of buprenorphine in the United States (2002-2008) has increased from 107 to 800,317 grams (~7,000 fold) [10]. An important underlying factor driving the increasing prescription rate for this drug is the perceived wider safety profile regarding respiratory suppression compared to other full μ-agonists such as methadone [11-15]. Based upon the most extensive worldwide experience in France, where general practitioners have been permitted to prescribe buprenorphine since 1996, the estimated yearly death rate (1994-1998) for methadone was at least three fold greater than the death rate related to buprenorphine [16, 17]. Although the death rate associated with methadone in the United States (2001-2006) has increased by 272%, the death rate for buprenorphine has not been specifically tracked [10]. In October 2002, the United

States Food and Drug Administration approved buprenorphine monotherapy (Subutex®) and a combination product of buprenorphine/naloxone (Suboxone®) for opioid detoxification therapy. Subutex® and Suboxone® are the first narcotic medications available for the treatment of opioid dependence that can be prescribed in a primary care office setting in the United States under the Drug Addiction Treatment Act of 2000 (Public Law 106-310) [18].

Despite the well known respiratory effects of μ-opioid agonists during sleep, we are unaware of any investigations of buprenorphine while subjects are sleeping except for a single case report in which buprenorphine was implicated as a cause of central sleep apnea [19]. Based upon our anecdotal experience, the true prevalence of sleep disordered breathing (SDB) and sleep-related hypoxemia associated with buprenorphine is likely to be substantial. However, in contrast to obstructive sleep apnea syndrome, there are presently no guidelines or standards regarding indications for performing polysomnography (PSG) in patients using opioids. Due to the potential lethality of chronic opioids and the lack of any specific risk factors that could be used to predict those who may have central sleep apnea, we implemented a care process model in which comprehensive polysomnography is a standard component of our inpatient opioid detoxification program when using buprenorphine (Suboxone® or Subutex®).

The purpose of this report is three fold: (1) to summarize the organization of our care process model; (2) to characterize the prevalence, severity and types of SDB in hospitalized patients receiving buprenorphine for detoxification from opioids; and (3) to identify potential risk factors that might be used in the future to select patients for testing.

METHODOLOGY:

Patient selection:

From November 2010 until August 2011, every patient admitted to an adult facility at the LDS Hospital (Day Spring) in Salt Lake City, Utah (elevation 1,500 m) for detoxification from opioid dependency using buprenorphine was eligible regardless of symptoms. The only limitation was unavailability of laboratory space.

Care Process Model:

In accordance with current practices, the induction phase of buprenorphine (Suboxone® or Subutex®) administration begins once the patient has abstained from using opioids for 12-24 hours and is in the early stage of withdrawal [13, 18, 20]. During the subsequent stabilization phase, at which time withdrawal symptoms have abated, a focused history and physical examination are obtained. The potential risks associated with chronic opioid therapy, the rationale for documenting the presence of sleep disordered breathing and possible subsequent respiratory therapy are discussed with the patient. Prior to beginning the maintenance phase and discharge, comprehensive monitored polysomnography is performed either in the sleep laboratory or on the psychiatry floor using wireless technology [21]. Therapy with positive airway pressure (usually adaptive servo-ventilation) and/or supplemental oxygen is provided according to current practices.

Polysomnography Studies: Standard attended 19-channel polysomnography (Cadwell Laboratories, Inc., Kennewick WA.) was performed and manually scored according to criteria established by the American Academy of Sleep Medicine [22]. Parameters consisted of frontal, central and occipital electroencephalogram, right and left electrooculogram, and submentalis electromyogram. Airflow was detected by nasal pressure transducers (PTAF II, Pro-Tech Services, Inc. Mukilteo, WA recorded in the DC mode (no filtering) and by oral-nasal thermistors (Thermisense 5700B, Salter Labs, Arvin, CA). Respiratory effort was determined by measurement of chest and abdomen motion with respiratory inductive plethysmography transducers which included a qualitative sum channel. Arterial oxygen saturation (SpO2) was measured by the Cadwell oximeter with a 4-beat averaging mode. Apneas were scored on the basis of absence of thermistor airflow for ≥ 10 seconds. Obstructive apneas were defined by the presence of respiratory effort; central apneas by the absence of respiratory effort. Hypopneas were defined as a ≥ 50% reduction in airflow for ≥ 10 seconds associated with ≥ 3% decrease in SpO2 or terminating EEG arousal. Hypopneas were not differentiated as obstructive or central. Apnea/Hypopnea index (AHI), Obstructive Apnea Index (OAI), Central Apnea Index (CAI) and Hypopnea Index (HI) were computed as the total of defined respiratory events divided by the total sleep time in hours (TST). Each record was scored simultaneously by two authors (RJF/JMW) for Biot's respiration or ataxic

breathing according to criteria previously published (Figure 1) [23]. Oximetry data was analyzed for mean SpO2, lowest SpO2 and time spent below 90% during sleep. In six patients who required supplemental oxygen due to severe hypoxemia that developed during polysomnography, only the initial room air portions of studies were used for computing respiratory statistics.

Statistical Analysis: Descriptive statistics consisting of means, standard deviation and ranges were derived for each sleep and respiratory measure. A random forest model was fit with AHI as the response variable and the buprenorphine dose, individual STOP-Bang indicators along with use of benzodiazepines, antidepressants, antipsychotics, and smoking history as the predictor variables. A random forest is a machine learning tool that models the response using many "trees" which are built using binary splits of the predictor variables [24-26]. A random forest will find non-linear and interaction relationships between the response and the predictors. This model was used as a first step to exploring possible relationships with the predictor variables. Separate random forests were fit with the same predictors but with AHI, CAI, OAI, HI, Ataxic breathing, mean SpO2, lowest SpO2, and percent of sleep below 90% as response variables. The relationship between the response variables and the individual predictors were also explored graphically. The Kolmogorov-Smirnov test was used to compare the 2 groups of outcomes with the group membership being determined by

benzodiazepines, antipsychotics, antidepressants, and cigarette smoking history (32 total tests) [27, 28].

RESULTS:

Study Population:

The subject characteristics are shown in Table 1. Typical risk factors for obstructive sleep apnea (OSA) were generally not found. The majority of patients were young (mean age ± SD = 31.8 ± 12.3 years), non-obese (mean BMI ± SD = 24.9 ± 5.9 kg/m^2) and female (60%). The STOP-Bang questionnaire, previously validated for screening pre-surgical patients for OSA, incorporates symptoms (snoring, tiredness, witnessed apneas and hypertension) with demographics (BMI, age, neck size and gender) [8]. A score ≥ 3 indicates a high probability of AHI > 5/hr (sensitivity 83.6%). Higher scores are correlated with more severe sleep apnea [29]. The STOP-Bang score (mean ± SD) measured 2.7 ± 1.2. A Mallampati score of 3 or 4 indicates the presence of a relatively small obstructive appearing pharyngeal lumen which may predispose to sleep disordered breathing, but the class does not predict severity [30]. The Mallampati score (mean ± SD) in this population measured 2.7 ± 0.7 (median 3).

Sleep Measures:

The results of sleep measurements are shown in Table 2. These data reflect the entire sleep record, with and without supplemental oxygen (6 and 64 patients respectively). Mean TST was somewhat reduced at 5.5 hours. The REM time as a percentage of TST (mean ± SD) measured 5.3 ± 6.7%. We have observed that some patients using opioids chronically present with strikingly unusual sleep

patterns characterized by sustained N2 non-REM sleep, being almost devoid of any awakenings with minimal to absent REM sleep (Figure 2).

Respiratory Measures:

The results of standard respiratory parameters are shown in Table 3. Various manifestations of SDB were common (i.e. apneas/hypopneas, hypoxemia and ataxic breathing rhythm). At least mild sleep disordered breathing (AHI ≥ 5/hr) was present in 63% of the group, consistent with previous reports of patients receiving chronic opioid therapy [2, 4]. Moderate (AHI ≥15 to < 30/hr) and severe sleep apnea (AHI ≥ 30/hr) was present in 16% and 17% respectively. Mean overall AHI was 20.4/hr with centrals apneas predominating (CAI 11.4/hr) with relatively few obstructive apneas (OAI 2.3/hr). Central apneas were more frequent in females than males (mean CAI 14.9/hr versus 6.3/hr respectively). The prevalence of ataxic breathing for the group measured 73%, similar to our previous report in which 70% of subjects mainly taking hydrocodone, oxycodone or methadone were observed to have ataxic respiration [2]. Moderate to severe ataxia was present in 20.0% and 18.6% respectively (38.6% overall).

The mean SpO2 while breathing room air during the study was 91.7% (normal for our elevation of 1500 m). Hypoxemia, defined as an SpO2 of < 90% for ≥ 10% of sleep time, was present in 27 (38.6%) and the lowest SpO2 nadir measured ≤ 85%

in 38 (54.3%). Of note, hypoxemia was present in 13 patients (28.2%) with AHI ≤ 15/hr.

Pharmacologic Data:

All but one patient was treated with combination buprenorphine/naloxone (Suboxone®). One was treated with buprenorphine (Subutex®). The amount of buprenorphine received before polysomnography ranged from 2.0 to 76.0 mg (mean ± SD total dose measured 18.5 ± 13.9 mg) with a target dose of 12-16 mg/day. When standardized to mg/hour (total mg received/total hours including the first and last dose before polysomnography), the time adjusted buprenorphine dose (mean ± SD) measured 0.4 ± 0.2 mg/hr. Since all these patients were hospitalized, multiple drugs were commonly used including benzodiazepines, neuroleptics, and muscle relaxants. None of these medications had an additive effect. There were no significant differences in the groups in the frequency of apneas, hypopneas, or measures of arterial oxygen saturation (Figure 3).

Statistical Analysis:

All of the random forest models showed little or no relationship between the predictor variables (e.g. BMI, gender and buprenorphine dose) and the response variables (i.e. apneas, hypopneas, ataxia and hypoxemia). The best fitting model was predicting mean SpO2 and that model only reduced the variability (compared to an overall mean) by 19%. This can be further seen in the graphical comparisons

where the distributions of the response variable are nearly identical between the groups determined by the drug usage (see online supplement). Further analysis with Kolmogorov-Smirnov tests showed that the unadjusted p-values ranged from 0.01 to 0.99999, with 5 being less than 0.05 (AHI by Smoking History, Mean SpO2 by Smoking History, Percent of sleep < 90% by Smoking History, AHI by antidepressants, and CAI by antidepressants). However, when the p-values were adjusted for multiple comparisons using the "False Discovery Rate" method the p-values then ranged from 0.22 to 0.99999 indicating that none of the differences were statistically significant [31].

DISCUSSION: The major findings from this study are: (1) clinically significant SDB occurred in many patients being initiated on buprenorphine/naloxone for opioid withdrawal therapy; (2) respiratory disturbances consisted predominantly of central apneas, ataxic breathing (Biot's respiration), and hypoxemia as seen with other opioids; (3) the presence and severity of breathing disturbances was not predicted by concomitant use of benzodiazepines or neuroleptics, buprenorphine dose or by standard risk factors for OSA; (4) recognition of SDB in these patients was enabled by incorporating routine comprehensive polysomnography into our inpatient opioid detoxification protocol.

The discovery of SDB in patients receiving buprenorphine should not be surprising however it is widely regarded as a "safe and effective opioid."[11, 13, 32] Furthermore, many clinicians may not be familiar with the unique pharmacologic profile of this particular opioid and its potential for respiratory toxicity [12, 20, 32, 33]. The biologic effects of all commercially available narcotics are mediated through μ-opioid-receptors with activation of classic G protein coupled receptors that stimulate intracellular inhibitory pathways of both pain and respiratory neurons [34]. The molecular mechanisms responsible for opioid tolerance and the expression of less than maximum biologic effects of partial agonists compared to full μ-opioid agonists are complex but polymorphism of the μ-opioid-receptors and the recently discovered regulators of G protein signaling may be involved [35, 36]. Genetic diversity of these mechanisms may

underlie the individual variability seen clinically regarding expression of respiratory toxicity. In general, chronic opioid use reduces respiratory drive, destabilizes pacemaker neurons that generate a regular breathing pattern during non-rapid eye movement sleep, and simultaneously disables the normal protective arousal responses to hypoxemia during sleep with potentially fatal consequences [5].

Buprenorphine is a potent partial μ-agonist (25-50 times greater than morphine) with very high receptor affinity (1000 times greater than morphine) and long dissociation half-life [12, 18]. Although it maintains an analgesic dose response across all levels, it appears to have a flat or U-shaped biologic response on respiratory suppression such that with increasing doses, it has a lower maximum or ceiling effect. In both animal and human studies, for example, the ventilatory response to hypercapnia does not continually decrease with progressively greater doses while the analgesic effect is maintained [11, 14, 15, 37-39]. Consequently, it is regarded as a safer opioid compared to methadone. However, buprenorphine is still a highly potent opioid with potentially profound respiratory effects occurring below the ceiling level (i.e. at doses typically used for detoxification or for analgesia) [39]. Therefore, buprenorphine is capable of causing significant respiratory disturbances during sleep like any other opioid. Furthermore, the respiratory toxicity of all opioids during sleep, but in particular buprenorphine, is under-appreciated because existing studies focus on acute and not chronic

administration, drugs are usually administered parenterally with measurements being performed during wakefulness, and the usual outcome measures are ventilatory responses to hypoxemia or hypercapnia. The effects of opioids on respiratory pattern generation during sleep or the arousal responses to hypoxemia and hypercapnia are not assessed.

There is a widely held view that respiratory depression resulting in fatal toxicity of buprenorphine is uncommon and when it occurs is linked with intravenous misuse and/or concomitant sedative drug ingestion, specifically benzodiazepines [10, 17, 40-42]. The putative mechanisms responsible for this interaction were recently reviewed by Mégarbane [32]. Gamma amino butyric acid (GABA) and opioid receptors are both co-expressed in brainstem locations associated with respiratory control and utilize common intracellular transduction pathways. A pharmacokinetic interaction resulting in altered drug levels has also been postulated however the exact mechanisms remain unclear. Consistent with our previous study [2], we did not find an increase in the AHI or measures of worse oxygenation when benzodiazepines or quetiapine were used within 24 hours of the polysomnogram as compared to those taking buprenorphine alone. Nevertheless, the potential for adverse interactions with any GABAergic drugs, including alcohol, that are likely to be taken concomitantly must be considered as a serious risk for developing more severe adverse respiratory effects.

The respiratory effects of opioids were manifest in three semi-autonomous domains: fundamental breathing pattern (ataxia versus regular breathing rhythm), breathing interruptions (apneas and hypopneas) and gas exchange (hypoxemia). The AHI is the most frequently reported outcome measure that defines the severity of sleep apnea. However, the effect of opioid exposure in many subjects was manifest as alteration of the basic breathing rhythm (i.e. ataxic or Biot's respiration), which may be very subtle and not necessarily associated with other definable respiratory events according to standard criteria. Hypoxemia was found in numerous cases with relatively trivial evidence of SDB as previously reported [43]. In this series, hypoxemia was present in 38.6% of the total group and in 28.2% of those with AHI < 15/hr. It should be stressed that there was a wide range of individual susceptibility with no clear predictive variables.

Limitations of study:

The presence of pre-existing underlying SDB unrelated to buprenorphine must be considered but the possibility that this is an important factor seems unlikely. As we previously demonstrated in patients with high risk factors for OSA who were also receiving chronic opioid therapy compared to a matched control population not taking opioids, non-periodic central apneas with unique ataxic breathing patterns were statistically more prevalent [2]. In the present study, the a priori risk for OSA was relatively low (mean STOP-Bang score 2.7), obstructive events were found in low frequency, the breathing patterns were most consistent with those

previously associated with chronic opioids therapy and there were no other risk factors for central disturbances. One could argue that SDB was related to residual effects of previous opioids; however, this seems highly unlikely since buprenorphine is only initiated during withdrawal states.

A second concern is that the respiratory events were influenced by other factors such as concomitant medications, especially benzodiazepines. It is almost impossible to completely control for drug interactions in such a clinical population however we were unable to demonstrate a statistically significant effect of various confounding factors on any domain of SDB. In addition to the density plots, which give a visual analysis, we were unable to demonstrate an interaction using quantitative statistics already discussed.

The present study was conducted at moderate elevation (1,500 m). Therefore, these findings, especially the degree of hypoxemia, may not apply to populations at lower elevations. The degree to which breathing rhythm disturbances or the propensity for developing central apneas at lower elevations is also uncertain. Finally, this was a short-term study with patients being studied generally within 48 hours after buprenorphine was initiated. The presence and severity of adverse respiratory effects occurring months later while receiving maintenance therapy are unknown; however, based upon previous experiences with other opioids being used chronically, it is unlikely that the respiratory suppressant effects would

resolve. We have no way of correlating the presence of respiratory abnormalities as described in this study with specific clinical outcomes or unexpected mortality. Evidence of an opioid effect could be seen in the majority of cases however the clinical significance of mild to moderate sleep apnea, hypoxemia or slight ataxic breathing is unknown without further studies.

Clinical implications:

Standard symptoms, demographic factors and buprenorphine dose are poor predictors of significant adverse respiratory effects. Consequently, all patients receiving buprenorphine should probably be monitored at least initially with some type of objective study. Routine comprehensive PSG in all cases is impractical, however limited cardiopulmonary sleep studies that incorporate SpO2 and respiratory pattern may be useful.

There is insufficient data from this study to support specific treatment recommendations. When the primary adverse effect is non-apneic hypoxemia, supplemental oxygen appears to be the most appropriate option. In patients who have frequent apneas and hypopneas, therapy with positive pressure should be considered especially if there are indications of increased airways resistance or obstructive events. Therapy with adaptive servo-ventilation appears to be effective in some cases but the efficacy of this modality remains controversial [23,

44]. Patients with mild opioid induced respiratory abnormalities are advised that they should be followed clinically.

Summary comments:

Prescriptions of buprenorphine have skyrocketed, presumably fueled by the perception that this opioid is safe because respiratory suppression is limited by the ceiling effect. Compared to methadone, use of buprenorphine seems to be less likely to result in fatal overdoses, however, there have been no systematic studies of the effects of buprenorphine on respiration during sleep until now. Our observations should raise concern about the potential for adverse and possibly lethal respiratory consequences during sleep using ordinary doses of buprenorphine.

TABLES:

Table 1. Demographics and possible risk factors for sleep disordered breathing

	Males (28)	Females (42)	All (70)
AGE (yrs)			
Mean (SD)	28.5 (9.3)	34.1 (13.6)	31.8 (12.3)
Range	18-53	19-73	18-73
BMI (kg/m^2)			
Mean (SD)	24.4 (4.7)	25.1 (6.6)	24.9 (5.9)
Range	15.3-37.9	16.2-41.0	15.3-41.0
Mallampati (1-4)			
Mean (SD)	2.9 (0.7)	2.6 (0.8)	2.7 (0.7)
Range	2.0-4.0	1.0-4.0	1.0-4.0
STOP-Bang (1-8)			
Mean (SD)	3.2 (1.1)	2.3 (1.2)	2.7 (1.2)
Range	1.0-6.0	0.0-6.0	0.0-6.0
Buprenorphine			
Total mg Mean (SD)	21.5 (17.5)	16.5 (10.7)	18.5 (13.0)
Range	2.0-76.0	2.0-48.0	2.0-76.0
mg/hr Mean (SD	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Range	0.1-1.1	0.1-1.1	0.1-1.1

Table 2. Sleep Measurements

	Males (28)	Females (42)	All (70)
TST (hrs)			
Mean (SD)	5.6 (1.2)	5.4 (1.2)	5.5 (1.2)
Range	2.5-7.3	1.9-7.7	1.9-7.7
N1 (% TST)			
Mean (SD)	12.7 (16.1)	9.0 (7.6)	10.4 (11.8)
Range	2.0-35.0	1.0-86.0	1.0-86.0
N2 (% TST)			
Mean (SD)	78.3 (16.4)	78.3 (12.8)	75.7 (14.6)
Range	45.0-98.0	14.0-95.0	14.0-98.0
N3 (% TST)			
Mean (SD)	8.8 (10.1)	8.5 (11.7)	8.6 (11.0)
Range	0.0-39.0	0.0-44.0	0.0-44.0
REM (% TST)			
Mean (SD)	6.6 (7.5)	4.3 (5.9)	5.3 (6.7)
Range	0.0-36.0	0.0-18.0	0.0-36.0

Table 2

Legend:

Abbreviations:

TST:	Total Sleep Time in hours
Stg N1:	Stage N1 of non-REM sleep as a percent of TST
Stg N2:	Stage N2 of non-REM sleep as a percent of TST
Stg N3:	Stage N3 of non-REM sleep as a percent of TST
Stg REM:	Stage REM sleep as a percent of TST

Table 3: Respiratory Measurements

	Males (28)	Females (42)	All (70)
AHI			
Mean (SD)	15.2 (26.3)	23.9 (35.6)	20.4 (32.3)
Range	0.0-106.2	0.0-180.0	0.0-180.0
CAI			
Mean (SD)	6.3 (19.0)	14.9 (32.6)	11.4 (28.1)
Range	0.0-176.4	0.0-97.6	0.0-176.4
OAI			
Mean (SD)	2.0 (2.3)	2.5 (4.7)	2.3 (3.9)
Range	0.0-8.6	0.0-26.5	0.0-26.5
HI			
Mean (SD)	6.9 (4.8)	6.5 (9.6)	6.6 (11.8)
Range	0.0-71.8	0.0-42.6	0.0-71.8
Baseline SpO2			
Mean (SD)	92.7 (3.0)	91.0 (3.5)	91.7 (3.4)
Range	86.0-98.0	83.0-98.0	83.0-98.0
% TST SpO2 < 90%			
Mean (SD)	13.4 (22.4)	29.8 (36.6)	23.2 (32.5)
Range	0.0-76.2	0.0-100.0	0.0-100.0

Table 3

Legend: See text for definitions.

Abbreviations:

AHI: Apnea/Hypopnea Index

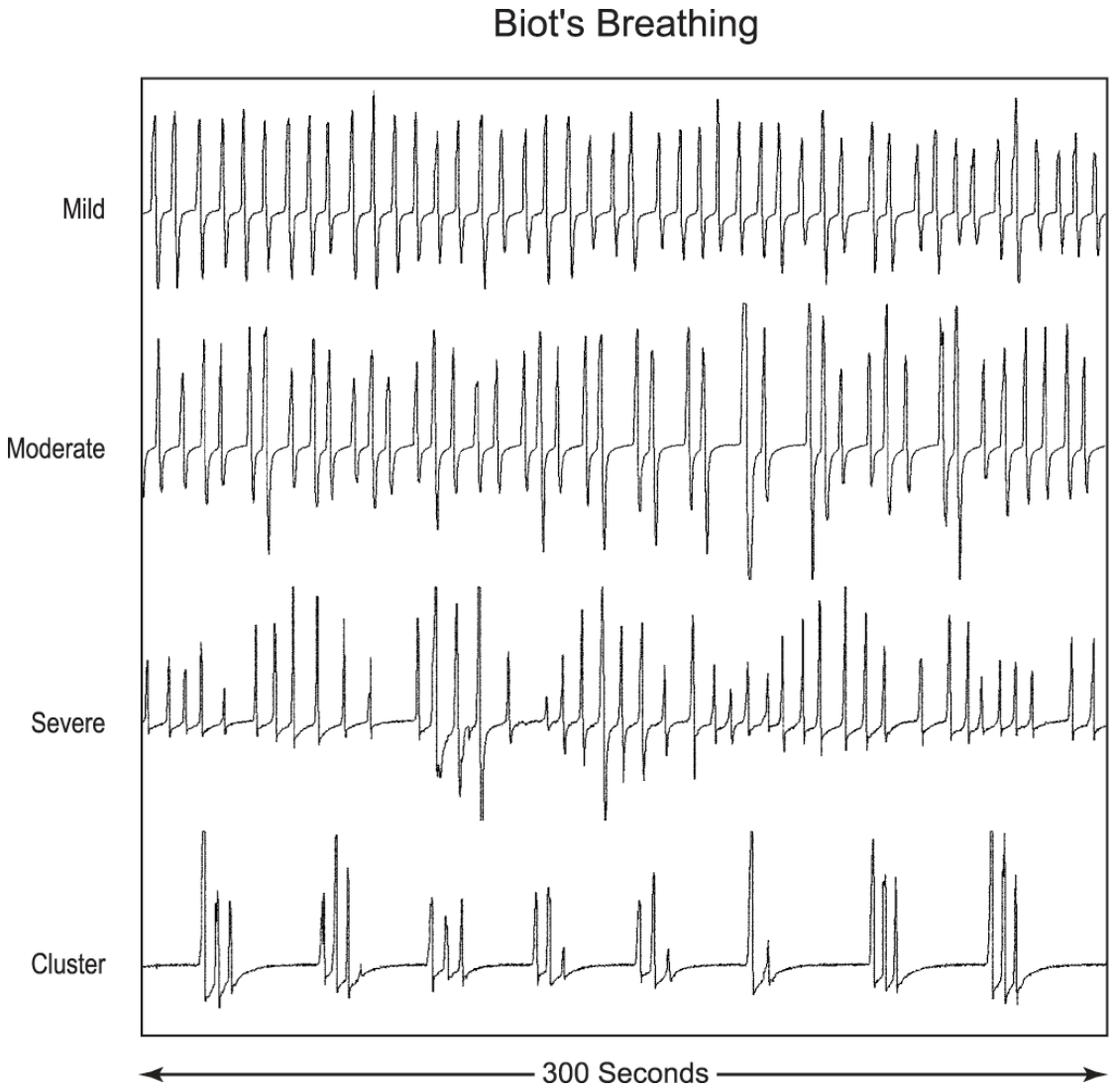
OAI: Obstructive Apnea Index

CAI: Central Apnea Index

HI: Hypopnea Index

FIGURES:

FIGURE 1:



Legend for Figure 1:

Variations of Biot's breathing patterns or ataxic respiration. Airflow patterns obtained from PTAF signals (air pressure) showing varying degrees of ataxic or irregular breathing (mild, moderate, and severe) plus an example of "cluster breathing" obtained from patients who were chronically receiving opioid medications. From Farney RJ, Walker JM, Boyle KM, et al. (2008) Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. Journal of Clinical Sleep Medicine 4(4): 311–319, with permission.

Figure 2A.

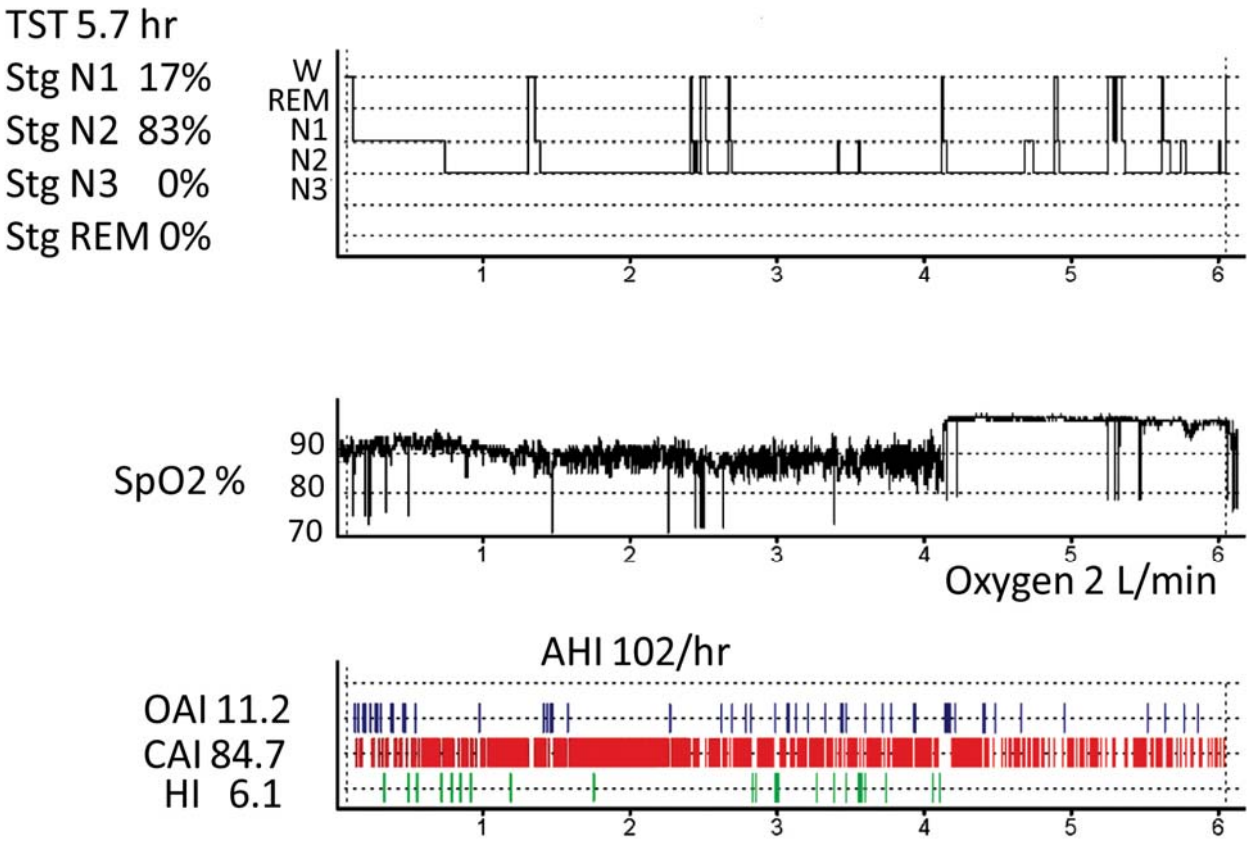

TST 5.7 hr
Stg N1 17%
Stg N2 83%
Stg N3 0%
Stg REM 0%
W
REM
N1
N2
N3
1
2
3
4
5
6
SpO2 %
90
80
70
Oxygen 2 L/min
AHI 102/hr
OAI 11.2
CAI 84.7
HI 6.1

Figure 2B.

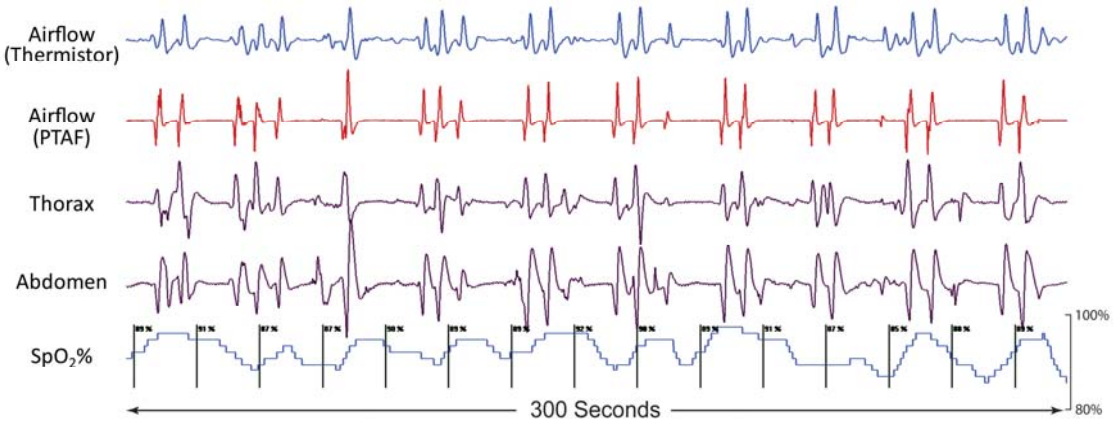

Airflow
(Thermistor)
Airflow
(PTAF)
Thorax
Abdomen
SpO2%
100%
80%
300 Seconds

Figure 2.

Legend: Figure 2A shows the sleep histogram and respiratory parameters from a patient with severe sleep disordered breathing. 62 year- female non-cigarette smoker with history of snoring, tiredness, hypertension and with BMI of 20 kg/m^2 (STOP-Bang score 4). Polysomnography was performed 25 hours after initiation of buprenorphine and having received a total dose of 6 mg. Medications included quetiapine, clorazepate, venlafaxine and omeprazole. Figure 2B shows a representative 300 second sample of raw data characterized by a predominance of cluster breathing or Biot's respiration and recurrent hypoxemia. Note the marked variability of underlying breathing pattern in terms of both rhythm and amplitude associated with oxygen desaturations. SpO2 measured less than 90% for 47.5% of sleep time with lowest nadir of 80%.

Abbreviations:

TST: Total Sleep Time in hours

Stg N1: Stage N1 of non-REM sleep as a percent of TST

Stg N2: Stage N2 of non-REM sleep as a percent of TST

Stg N3: Stage N3 of non-REM sleep as a percent of TST

Stg REM: Stage REM sleep as a percent of TST

AHI: Apnea/Hypopnea Index

OAI: Obstructive Apnea Index

CAI: Central Apnea Index

HI: Hypopnea Index

Figure 3 A

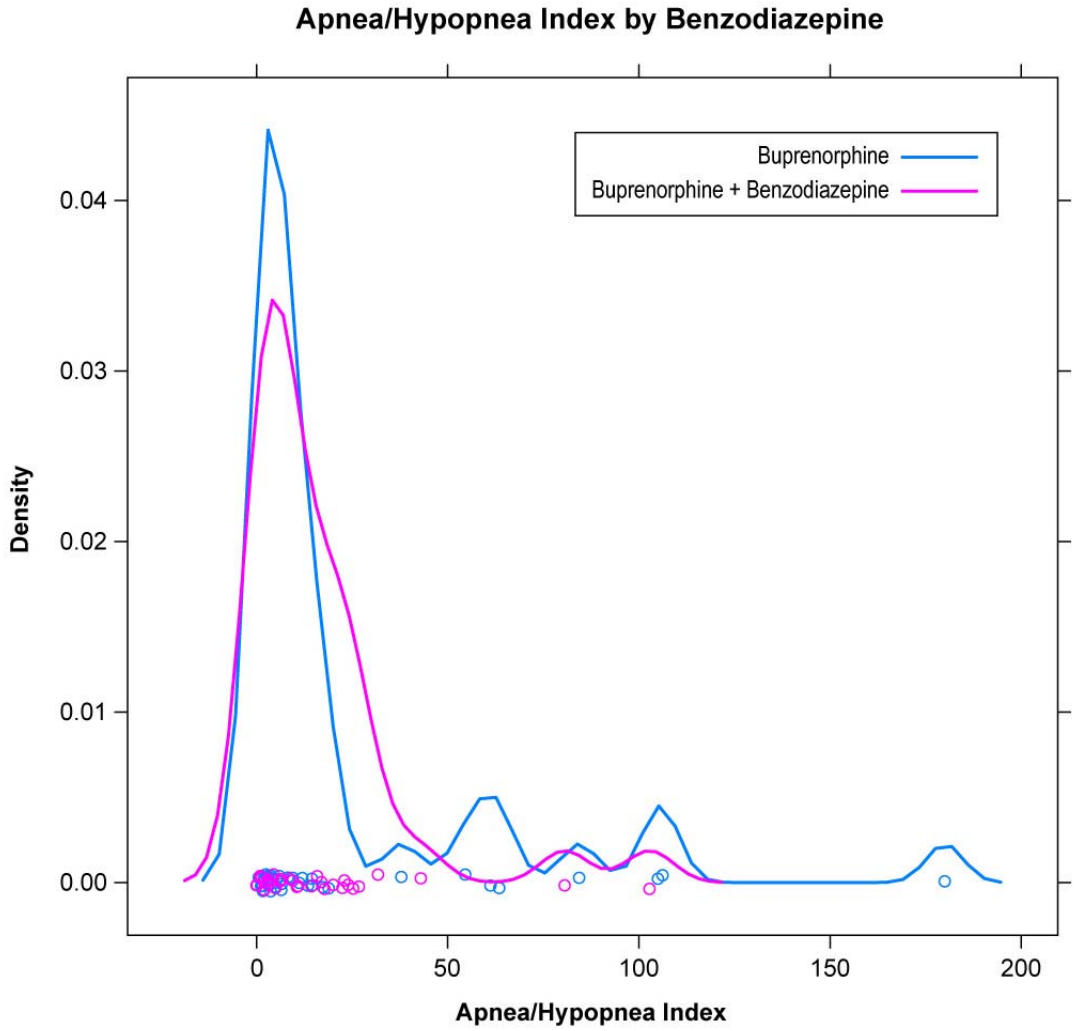

Apnea/Hypopnea Index by Benzodiazepine
Buprenorphine
Buprenorphine + Benzodiazepine
Density
0.04
0.03
0.02
0.01
0.00
0
50
100
150
200
Apnea/Hypopnea Index

Figure 3 B

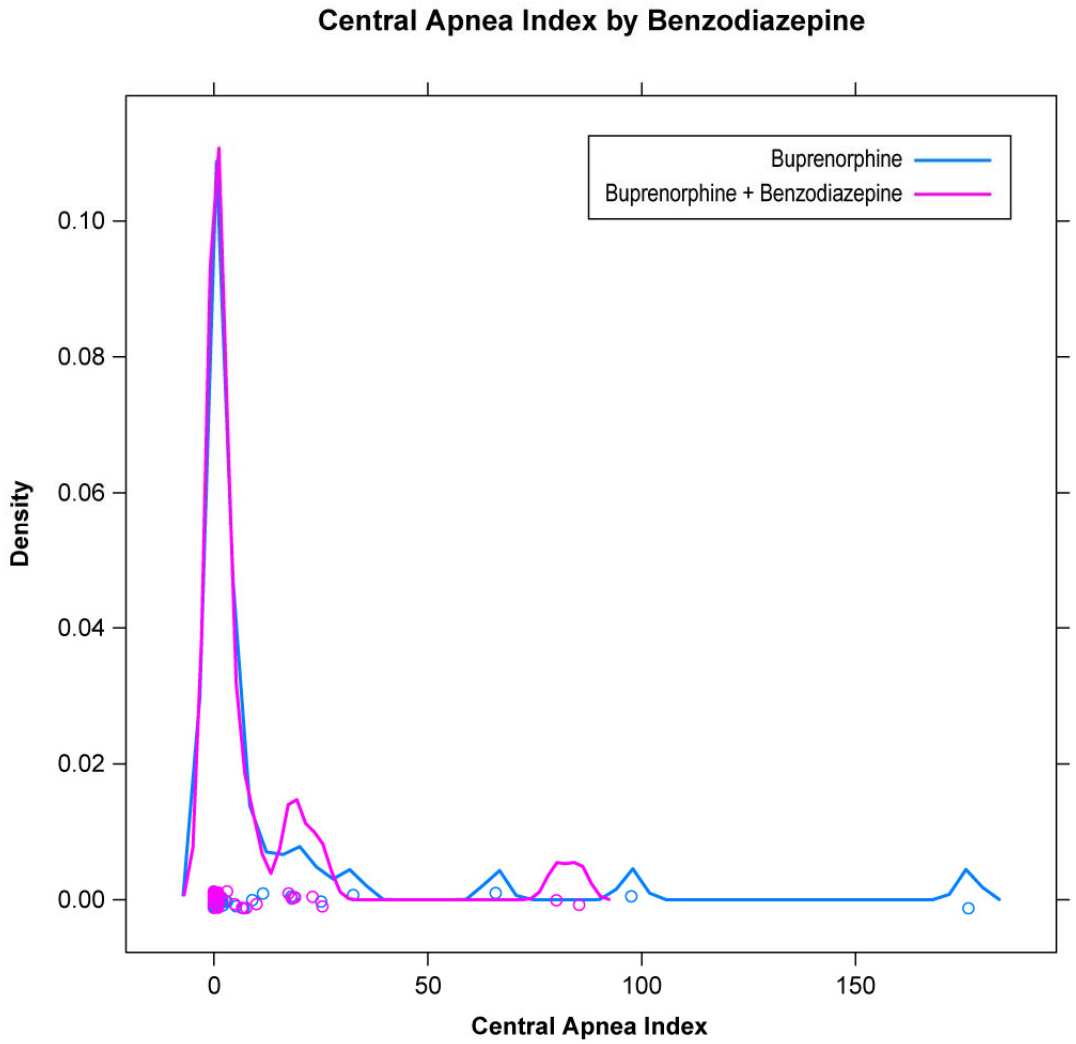

Central Apnea Index by Benzodiazepine
Buprenorphine
Buprenorphine + Benzodiazepine
Density
0.10
0.08
0.06
0.04
0.02
0.00
0
50
100
150
Central Apnea Index

Figure 3 C

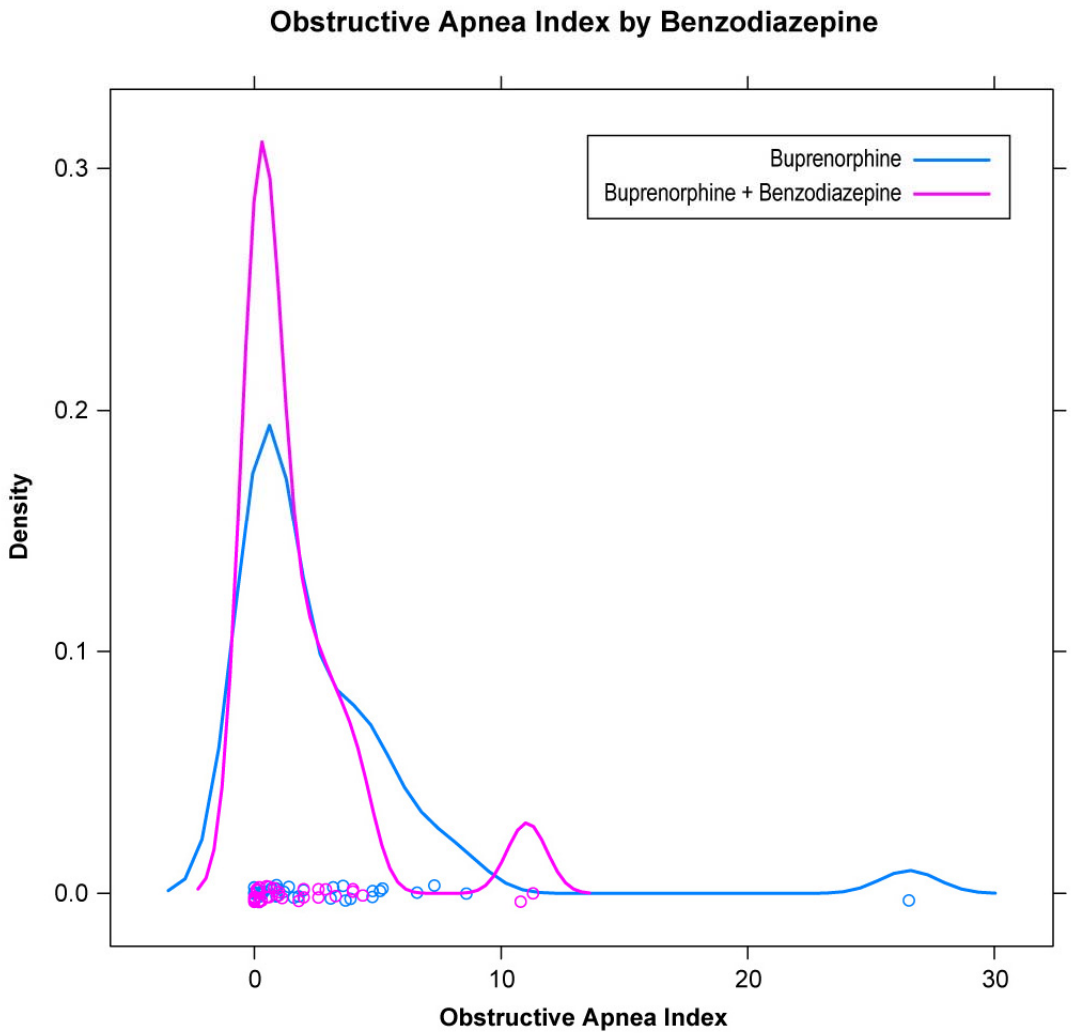

Obstructive Apnea Index by Benzodiazepine
Buprenorphine
Buprenorphine + Benzodiazepine
Density
0.0
0.1
0.2
0.3
0
10
20
30
Obstructive Apnea Index

Figure 3

Legend: These probability distribution graphs show kernel density estimates of AHI, OAI, and CAI separate for those receiving and not receiving benzodiazepines [45]. The overlap of the 2 curves within each subplot shows that there is no real practical difference in the outcome between the 2 groups. Similar plots showed the same similarity with the other potential predictors on this group of subjects (see on-line supplement for all comparisons and correlations).

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