Sleep-Disordered Breathing and Chronic Opioid Therapy

Lynn R. Webster, MD,* Youngmi Choi, MD, PhD,† Himanshu Desai, MD,‡† Linda Webster, RPSGT,§ and Brydon J. B. Grant, MD†‡¶

*Lifetree Clinical Research and Pain Clinic, Salt Lake City, Utah, USA; †Departments of Medicine, ‡Physiology and Biophysics, Social and Preventive Medicine and Biostatistics, University at Buffalo SUNY, §Medical One Medical, Sandy, Utah USA; and ¶Veteran Affairs Healthcare System, Buffalo, New York, USA

ABSTRACT

Objective. To assess the relation between medications prescribed for chronic pain and sleep apnea.

Design. An observational study of chronic pain patients on opioid therapy who received overnight polysomnographies. Generalized linear models determined whether a dose relation exists between methadone, nonmethadone opioids, and benzodiazepines and the indices measuring sleep apnea.


Patients. Polysomnography was sought for all consecutive (392) patients on around-the-clock opioid therapy for at least 6 months with a stable dose for at least 4 weeks. Of these, 147 polysomnographies were completed (189 patients declined, 56 were directed to other sleep laboratories by insurance companies, and data were incomplete for seven patients). Available data were analyzed on 140 patients.

Outcome Measures. The apnea–hypopnea index to assess overall severity of sleep apnea and the central apnea index to assess central sleep apnea.

Results. The apnea–hypopnea index was abnormal (≥5 per hour) in 75% of patients (39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea); 25% had no sleep apnea. We found a direct relation between the apnea–hypopnea index and the daily dosage of methadone (P = 0.002) but not to other around-the-clock opioids. We found a direct relation between the central apnea index and the daily dosage of methadone (P = 0.008) and also with benzodiazepines (P = 0.004).

Conclusions. Sleep-disordered breathing was common in chronic pain patients on opioids. The dose–response relation of sleep apnea to methadone and benzodiazepines calls for increased vigilance.

Key Words. Obstructive Sleep Apnea; Central Sleep Apnea; Complex Sleep Apnea; Ehronie Nonmalignant Pain; Opioids; Methadone

Introduction

Opioids are an effective tool for the treatment of intractable pain, and their long-term administration to patients with chronic nonmalig-
nant pain continues to gain widespread acceptance. Pain relief via around-the-clock opioid therapy is being delivered by a greater number of primary care physicians and other nonspecialists than ever before.

Recent increases in unintentional overdose deaths have been reported in several states [1–3]. Many of these deaths are associated with methadone, a drug with a large documented increase as a medication prescribed for pain in recent years [3]. The reasons for the increased deaths are unclear, but opioids could raise the risk of sleep apnea, which may impact morbidity and mortality in chronic pain patients. In one study, 30% of opioid-tolerant patients in a methadone maintenance treatment center experienced central sleep apnea [4]. These reports, together with a case series of three chronic pain patients on long-term opioid therapy who exhibited sleep-disordered breathing [5], stimulated the current study to assess the potential prevalence of central and obstructive sleep apnea in opioid-treated pain patients.

**Methods**

**Subject Selection**

Because of concerns about increased unintentional overdose deaths involving pain medications, all patients seen at Lifetree Pain Clinic who were on around-the-clock opioid therapy for at least 6 months were asked to undergo overnight polysomnography regardless of whether or not they exhibited risk factors or symptoms suggesting sleep apnea. Patients were considered to be on around-the-clock opioids if they regularly used short-acting opioids four or more times equally distributed throughout a 24-hour period, were on sustained-release opioids or both. Long-acting opioids and sustained-release opioids were considered the same for the purposes of this study. All patients had been on opioids for at least 6 months, and the daily dose had been stable for at least 4 weeks.

A total of 392 consecutive patients were asked to undergo a diagnostic polysomnography. Of these patients, 147 polysomnographies were completed at Medical One Medical sleep laboratory in Sandy, Utah (189 patients declined, 56 were directed to other sleep laboratories by insurance companies, and data were incomplete for seven patients). Therefore, we analyzed available data on 140 chronic pain patients on around-the-clock opioid therapy who had undergone polysomnography between February 2004 and July 2005.

Patient demographics were collected, including age, gender, race, body mass index (BMI), disease history, family history and primary pain diagnosis. Other patient parameters collected included average pain score, daily oral morphine equivalent, and number of concomitant central nervous system-depressant medications.

**Polysomnography**

All patients underwent standard overnight polysomnography with recordings of electroencephalogram, electrooculogram, submental and bilateral leg electromyograms, and electrocardiogram. Airflow was measured qualitatively by an oral–nasal thermistor or nasal pressure and respiratory effort by thoracoabdominal piezoelectric belts. Measurement of arterial oxyhemoglobin saturation was performed with 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).

Sleep stages were scored in 30-second epochs using standard criteria [6]. The record was analyzed for the number of apneas, hypopneas, electroencephalogram arousals, oxyhemoglobin desaturations, and disturbances in cardiac rate and rhythm. Apnea was defined as the absence of airflow for at least 10 seconds. The apnea was defined as obstructive if respiratory effort was present, central if respiratory effort was absent, and mixed if both features were present. Hypopnea was defined as a visible reduction in airflow lasting at least 10 seconds and associated with either a 3% decrease in arterial oxyhemoglobin saturation or an electroencephalogram arousal. An arousal was defined according to criteria proposed by the Atlas Task Force [7]. Central apneas were inspected to determine whether they conformed to the Cheyne–Stokes respiration with its periodic crescendo–decrescendo pattern of tidal volume.

Three indices were derived. The apnea–hypopnea index, a measure of overall severity of sleep apnea, was defined as the number of apneas and hypopneas per hour of sleep. The central apnea index was defined as the number of central sleep apneas per hour of sleep. The obstructive/mixed apnea index was defined as the number of obstructive and mixed apneas per hour of sleep.

Patients were classified as having obstructive sleep apnea if the apnea–hypopnea index was ≥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 ≥5 events per hour. If this difference was <5 
events per hour, the type of sleep apnea was clas-
sified as indeterminate. Patients were classified as 
having central sleep apnea if the central apnea 
index was ≥5 events per hour and the obstructive/
mixed apnea index was <5 events per hour, and 
both central and obstructive sleep apnea if the 
central apnea index and the obstructive/mixed 
apnea index were ≥5 events per hour.

The level of severity was classified as follows: 
mild apnea–hypopnea index 5 to <15 events per 
hour; moderate apnea–hypopnea index 15 to <30 
events per hour; and severe apnea–hypopnea index 
≥30 events per hour.

All patients were prescribed around-the-clock 
opioids. Four percent were on methadone alone, 
67% were on opioids other than methadone, and 
29% were on methadone and other opioids. These 
nonmethadone opioid preparations were oxyc-
odone (69%), hydrocodone (32%), fentanyl 
(26%), morphine (21%), hydromorphone (4%), 
and tramadol (3%). Opioids were converted to 
morphine equivalents [8]. Benzodiazepines (in 
36% of patients) were converted to diazepam 
equivalents [9].

Data Analysis
To test the effects of medication on sleep apnea, 
we focused on two measures: the apnea–hypopnea 
index and the central apnea index. We determined 
which drug groups were associated with these two 
indices. Both indices and the daily dosages of mor-
phine and diazepam equivalents were transformed 
logarithmically (log10([x + 1])) so that they would 
more closely conform to a normal distribution and 
to avoid the influence of extreme values.

Generalized linear models were used to deter-
mine if dose–response relations were observed 
between the apnea–hypopnea and central apnea 
indices and the use of methadone, nonmethadone 
opioids, and benzodiazepines. The models were 
adjusted for potentially confounding factors: age, 
BMI, gender, and other drug groups that were 
shown to have an effect in the exploratory analysis. 
Lack of collinearity was confirmed from correla-
tion coefficients.

Statistical analyses were conducted using Splus 
version 7.0 (Insightful Corp, Seattle, WA). Confi-
dence intervals were calculated with confidence 
interval analysis [10]. Statistical significance was 
accepted at the 5% level. This study was approved 
by the institutional review board at the Veteran 
Affairs Medical Center in Buffalo, NY.

Results
The mean age of the 140 patients was 51 years 
(range 22–84), and the mean BMI was 29.7 kg/m². 
The female-to-male ratio was 1.51 to 1. The most 
common reason for around-the-clock opioid ther-
apy was lumbar pain (60%), followed by thoraco-
abdominal pain and limb pain (8% each), cervical 
pain and headache (7% each), myalgia (6%), and 
miscellaneous causes (4%).

All patients were taking opioid medications, but 
not all took methadone (Table 1). Other drugs 
were categorized into various groups: nonsteroidal 
algesics, benzodiazepines, antidepressants, mus-
cle relaxants, anticonvulsants, stimulants, anti-
histaminics, and proton pump inhibitors. The 
patients were coded as to whether or not they were 
taking drugs in the groups just mentioned: 1 for 
yes and −1 for no. This effects coding system was 
used to avoid introducing collinearity.

The median daily dosage of all opioids was 
266 mg of morphine equivalents (range 15–5,985 mg). 
In the 33% of patients taking methadone, the 
median daily dosage of morphine equivalents was 
187.5 mg/day (range 18.75–1,500 mg/day). The 
median daily dosage of sustained-release opioids 
other than methadone in morphine equivalents was 
187.5 mg/day (range 15–5,085 mg/day). In 36% of 
patients taking benzodiazepines, the median daily 
dosage in diazepam equivalents was 15 mg/day 
(range 1.25–80 mg/day).

The sleep apnea characteristics of these patients 
are shown in Table 2. Abnormal apnea–hypopnea 
index was recorded for 75% of patients, while 25% 
had no sleep apnea. Of those with abnormalities, 
39% had obstructive sleep apnea, 4% had sleep 
apnea of indeterminate type, 24% had central

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Medication usage of the patients expressed as percentage of the sample (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Mean</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Methadone and other opioids</td>
<td>29</td>
</tr>
<tr>
<td>Methadone as sole opioid</td>
<td>4</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>36</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>36</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>34</td>
</tr>
<tr>
<td>Nonsteroidal analgesics</td>
<td>11</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>28</td>
</tr>
<tr>
<td>Stimulants</td>
<td>16</td>
</tr>
<tr>
<td>Antihistaminics</td>
<td>4</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>8</td>
</tr>
</tbody>
</table>

The sleep disorders and opioids characteristics of these patients are shown in Table 2. Abnormal apnea–hypopnea index was recorded for 75% of patients, while 25% had no sleep apnea. Of those with abnormalities, 39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central...
sleep apnea, and 8% had both central and obstructive sleep apnea. None of the patients with central sleep apnea demonstrated Cheyne–Stokes respiration. Although respiration was sometimes periodic in severe cases, there was no crescendo–decrescendo pattern of tidal volume.

Table 3 shows the relation of medication usage (expressed as dichotomous variables) to the apnea–hypopnea index and the central apnea index, adjusted for age, gender, and BMI. Three variables showed statistically significant relations to the apnea–hypopnea index: methadone use ($P = 0.007$), intake of muscle relaxants ($P = 0.034$), and BMI ($P = 0.045$). Only methadone ($P = 0.004$) and benzodiazepine ($P = 0.042$) use were significant for the central apnea index.

Table 4 shows a dose–response relation between the apnea–hypopnea index and methadone morphine equivalents ($P = 0.002$). A dose–response relation was found between the central apnea index and methadone morphine equivalents ($P = 0.008$) and with diazepam equivalents ($P = 0.004$). The dose–response relation was adjusted for age, gender, and BMI and also for use of muscle relaxants because this variable was significant in the preceding analysis. No dose–response relation was found between either index and nonmethadone opioids.

Twenty polysomnography studies were selected using a random number generator for rescoring to test the reliability of the scoring of the apnea–hypopnea index and the central apnea index. The scorer was blinded to the original test results. The mean difference between the original and rescored value of the apnea–hypopnea index was $-3.8$ per hour (95% CI: 6.9 to $-0.8$ per hour), and the mean difference for the central apnea index was 3 per hour (95% CI: 0.4–5.5 per hour). Of the 20 rescored, only one (5%) showed a clinically important difference (the central apneas were rescored as mixed apneas resulting in the patient being classified as having obstructive rather than central sleep apnea).

**Discussion**

The results show an extraordinarily high prevalence of sleep-disordered breathing in opioid-treated chronic pain patients. Obstructive and central sleep apnea syndromes occurred in the studied population at a far greater rate (75%) than is observed in the general population, where obstructive sleep apnea is known to be underdiag-

### Table 2 Sleep apnea characteristics of the patients expressed as percentage of the sample ($n = 140$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI $\geq$ 5 events/hour</td>
<td>75</td>
<td>68–82</td>
</tr>
<tr>
<td>AHI $\geq$ 15 events/hour</td>
<td>50</td>
<td>42–58</td>
</tr>
<tr>
<td>AHI $\geq$ 30 events/hour</td>
<td>36</td>
<td>29–45</td>
</tr>
<tr>
<td>CAI $\geq$ 5 events/hour</td>
<td>33</td>
<td>25–41</td>
</tr>
<tr>
<td>CAI $\geq$ 15 events/hour</td>
<td>23</td>
<td>16–30</td>
</tr>
<tr>
<td>CAI $\geq$ 30 events/hour</td>
<td>14</td>
<td>8–19</td>
</tr>
<tr>
<td>OMAI $\geq$ 5 events/hour</td>
<td>34</td>
<td>26–42</td>
</tr>
<tr>
<td>OMAI $\geq$ 15 events/hour</td>
<td>11</td>
<td>6–17</td>
</tr>
<tr>
<td>OMAI $\geq$ 30 events/hour</td>
<td>5</td>
<td>2–10</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>39</td>
<td>31–47</td>
</tr>
<tr>
<td>Central sleep apnea</td>
<td>24</td>
<td>17–31</td>
</tr>
<tr>
<td>Both central and obstructive sleep apnea</td>
<td>8</td>
<td>4–14</td>
</tr>
<tr>
<td>Sleep apnea: type indeterminate</td>
<td>4</td>
<td>1–8</td>
</tr>
</tbody>
</table>

AHI = apnea–hypopnea index; CAI = central apnea index; OMAI = obstructive and mixed apnea index.

### Table 3 Effect of medications on apnea–hypopnea index and central apnea index: multivariable models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apnea–hypopnea index</th>
<th>Central apnea index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
</tr>
<tr>
<td>Age</td>
<td>-0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.055</td>
<td>0.051</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.014</td>
<td>0.007</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.075</td>
<td>0.052</td>
</tr>
<tr>
<td>Nonsteroidal analgesics</td>
<td>0.042</td>
<td>0.075</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>-0.118</td>
<td>0.055</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>0.081</td>
<td>0.051</td>
</tr>
<tr>
<td>Antihistaminics</td>
<td>-0.107</td>
<td>0.147</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0.006</td>
<td>0.065</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>-0.046</td>
<td>0.088</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.139</td>
<td>0.051</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>0.044</td>
<td>0.050</td>
</tr>
</tbody>
</table>

* $P < 0.05$.

Age (years) and body mass index (kg/m$^2$) were continuous variables. All remaining variables were dichotomous and coded: 1 for male and –1 for female; or 1 for yes and –1 for no for each of the other variables indicating usage of a drug group. Both apnea–hypopnea index and central apnea index were logarithmically transformed.
nosed but has been estimated at roughly 2% to 4% [11]. Central apnea is estimated at 5% in people older than 65 years [12] and from 1.5% to 5% in men less than 65 years old [13]. Sleep studies included in the analysis were obtained in 140 out of the total of 392 patients for whom a study was sought. Even if none of the un-analyzed patients had sleep apnea, the prevalence would still be high at 27%. The association observed between methadone treatment and the severity of sleep apnea, along with the additive effect of the combination of methadone and benzodiazepines on the severity of central sleep apnea, have not been previously reported.

A striking component of the current study is the atypical pattern of central sleep apnea. Much sleep apnea is associated with Cheyne–Stokes respiration, common in patients with cardiovascular disease and stroke and characterized by a crescendo–decrescendo breath size. The breathing pattern of central sleep apnea observed in this study was not of the Cheyne–Stokes pattern, suggesting the mechanism for central sleep apnea in this population is different. It may be related to the direct effects of opioids on the respiratory controller [14].

**Opioids and Sleep**

It is widely accepted that patients who require chronic opioid therapy should be placed on around-the-clock opioids supplemented, if necessary, with short-acting opioids to control breakthrough pain. This approach is thought to provide better control of persistent pain throughout the day and night in part by facilitating uninterrupted sleep. However, few experimental studies have been performed to assess the effects of opioids on sleep in patients with pain.

One pharmaceutical industry-supported study reported improved sleep quality in patients with chronic pain on 30 mg/day of sustained-release morphine administered in the morning [15]. In contrast, a different study found that intravenous morphine decreased the time spent in slow-wave and rapid eye movement (REM) sleep and increased non-REM stage 2 sleep without changing total sleep time in seven healthy nonaddicts treated for acute pain [16]. The investigators emphasize, however, that patients with prior exposure to opioids demonstrate a different arousal response to morphine, making it difficult to draw conclusions about morphine’s nocturnal effects in various clinical populations.

Additional literature has suggested that sleep disturbances occur commonly with opioid use and chronic pain [17]. Three patients on sustained-release opioids for chronic pain demonstrated distinct patterns of sleep-disordered breathing, including ataxic breathing, central apneas, sustained hypoxemia, and prolonged obstructive hypopneas [5]. The respiratory disturbances occurred predominantly and lasted longer during non-REM sleep than during REM sleep, contrary to what is usually observed with obstructive sleep apnea. Why this occurred remains unclear.

**Methadone**

In the current study, a direct relation was found between the apnea–hypopnea index and methadone (Tables 4, \( P = 0.002 \)), but no relation was established with other around-the-clock opioids even though both daily dosages were equal as morphine equivalents. Increased dosage of methadone was associated with more severe sleep apnea. This is an interesting finding. The cause of this association is unclear but may be associated with

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apnea–hypopnea index</th>
<th>Central apnea index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.000</td>
<td>−0.002</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.065</td>
<td>0.026</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.013</td>
<td>−0.003</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>0.107</td>
<td>0.247</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.138</td>
<td>0.130</td>
</tr>
<tr>
<td>Nonmethadone opioids</td>
<td>0.113</td>
<td>0.073</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>−0.109</td>
<td>−0.104</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \).

Age (years) and body mass index (kg/m²) were continuous variables. Gender and muscle relaxants were dichotomous and coded as: 1 for male and −1 for female; 1 for yes and −1 for no, respectively. Both the apnea–hypopnea index and the central apnea index were logarithmically transformed. Benzodiazepines were the logarithmically transformed daily dose expressed as diazepam equivalents (mg/day). Methadone and nonmethadone opioids were the logarithmically transformed daily dose expressed as morphine equivalents (mg/day).
methadone’s N-methyl d-aspartate antagonist properties, which prevent opioid tolerance [18]. If tolerance is delayed or incomplete, then tolerance to the respiratory-depressant effects of methadone may also be delayed or incomplete and thus impart more vulnerability to sleep apnea.

Although the statistical analysis in the current study isolates methadone (and also methadone combined with benzodiazepines) as a contributor to increased apnea prevalence, the analysis is not yet adequate to exclude administration of non-methadone opioids as an independent risk factor.

**Benzodiazepines**

Benzodiazepines appeared to have an additive effect to the prevalence of methadone-related central sleep apnea. Because all patients were taking opioids, the effects of benzodiazepines alone could not be assessed. It is possible that benzodiazepines act as an effect modifier but have no direct effect alone.

Benzodiazepines are known to blunt the arousal response to hypoxia and hypercapnia during sleep [19], and limited research suggests they may worsen sleep-disordered breathing in patients with pulmonary or cardiac disease [13]. Other research indicates that benzodiazepines exert a large influence on the variability of blood methadone concentration and could possibly inhibit the metabolism of methadone, prolonging its effect [20]. Considering the frequent consumption of benzodiazepines among patients with chronic pain, it is important to isolate and understand benzodiazepines’ mechanism in this context.

**Pain and Other Risk Factors**

Chronic pain and sleep disturbances frequently occur together, although it is unclear whether they are causally related or represent two separate disorders [17]. More than 70% of patients suffering from painful disorders also report disturbances in sleep [16]. Pain conditions make sleep difficult, and shortened sleep increases hyperalgesic response the next morning [17,21]. Furthermore, sleep rebound, particularly non-REM sleep rebound, may induce an analgesic effect [17]. Thus, it appears that pain and disordered sleep may potentiate each other.

Sleep disturbances also are common secondary to chronic opiate use in the absence of pain [17]. The potential for opioids to worsen sleep disorders is difficult to isolate in the presence of chronic pain.

The chronic pain population may exhibit some characteristics that make them more vulnerable to sleep apnea—perhaps the population is more sedentary and has higher BMIs, for example. The current study found a greater apnea–hypopnea index (but not central apnea index) in higher BMI categories. This observation is concordant with a higher prevalence of accidental overdose deaths—many of which involved prescription opioids—in high BMI patients compared with those with low BMI [22]. It is imperative to identify the vulnerability factors given the increase in the administration of long-acting opioids and the high prevalence of undiagnosed sleep apnea.

The inverse relation observed with muscle relaxants to the apnea–hypopnea index is surprising. It may be that those patients requiring muscle relaxants have increased tone, which protects the upper airway from collapse.

**Limitations**

This study is limited in several ways. The cross-sectional sample from one pain clinic may not be representative, and the retrospective, observational method is liable to selection bias. The retrospective nature of the study made it difficult to characterize the patients who did not report for a sleep study. The concept of equianalgesic doses of different opioids is based on analgesic effects of opioids in an acute pain model and may have little correlation when used chronically. Furthermore, no studies show the equianalgesic equivalents of methadone to other opioids. At best, an estimate was used. Finally, it was assumed that the dosage of drugs taken was as prescribed. Methadone is less likely to be diverted illegally, which may account for the direct dose–response relation for this drug and not the nonmethadone opioids. However, the study sample consisted of long-term patients who were stable on opioids, and diversion of opioids is less likely in this type of population.

**Concluding Remarks**

The data suggest that opioids, in particular methadone, may be related to sleep apnea in chronic pain patients. This observation deserves further investigation as a possible public safety concern. The challenge is to monitor and adjust medications for maximum safety, not to eliminate them at the expense of pain management.

**Acknowledgments**

Data collection performed by Medical One Medical, Sandy, Utah. Technical writing and manuscript review were provided by Beth Dove.
References


Appendix

Opioids were converted to the equivalent oral morphine dose (mg) by multiplying the daily dosage of
the opioid by the designated multiplier for each type of opioid given in the following table.

**Table A1  Calculation of morphine equivalents**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Multiplier for equivalent oral morphine dose (mg)</th>
<th>Opioid</th>
<th>Multiplier for equivalent oral morphine dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodeone*</td>
<td>1</td>
<td>Codeine*</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydrocodeone*</td>
<td>1</td>
<td>Propoxyphene**</td>
<td>0.2</td>
</tr>
<tr>
<td>Hydromorphone*</td>
<td>4</td>
<td>Buprenorphine††</td>
<td>50</td>
</tr>
<tr>
<td>Methadone (Chronic)*</td>
<td>3.75</td>
<td>Tramadol††</td>
<td>0.2</td>
</tr>
<tr>
<td>Fentanyl (Transdermal)†</td>
<td>20.8</td>
<td>Butorphanol**</td>
<td>5</td>
</tr>
<tr>
<td>Fentanyl (Oral)‡</td>
<td>37.5</td>
<td>Morphine (Intravenous)§</td>
<td>3</td>
</tr>
<tr>
<td>Levorphanol§</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Calculated using http://www.globalrph.com/narcoticonv.htm
‡ MD Anderson hospital recommendation, see link http://utmext01a.mdacc.tmc.edu/mda/cm/CWTGuide.nsf/0/146c6f7a8a4352f8625685d0074c26/$FILE/Ca%20Pain%20V4%20group.pdf
¶ Cancer Control 2000; 132–141.

Benzodiazepines were converted to the equivalent oral diazepam dose (mg) by multiplying the daily
dosage of the opioid by the designated multiplier for each type of benzodiazepine given in the following

**Table A2  Calculation of diazepam equivalents**

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Multiplier for equivalent diazepam dose (mg)</th>
<th>Benzodiazepine</th>
<th>Multiplier for equivalent diazepam dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>20</td>
<td>Loprazolam</td>
<td>6.66</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>1.82</td>
<td>Lorazepam</td>
<td>10</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>0.4</td>
<td>Lorometazepam</td>
<td>6.66</td>
</tr>
<tr>
<td>Clobazam</td>
<td>0.5</td>
<td>Medazepam</td>
<td>1</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>20</td>
<td>Nitrazepam</td>
<td>1</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>0.66</td>
<td>Nordazepam</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1</td>
<td>Oxazepam</td>
<td>0.5</td>
</tr>
<tr>
<td>Estazolam</td>
<td>6.6</td>
<td>Prazepam</td>
<td>0.66</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>10</td>
<td>Quazepam</td>
<td>0.5</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>0.44</td>
<td>Temazepam</td>
<td>0.5</td>
</tr>
<tr>
<td>Halazepam</td>
<td>0.5</td>
<td>Triazolam</td>
<td>20</td>
</tr>
<tr>
<td>Ketazolam</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonbenzodiazepines with similar effects</td>
<td>0.5</td>
<td>Zolpidem</td>
<td>0.5</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: http://www.benzo.org.uk/manual/bzcha01.html#24
Copyright of Pain Medicine is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.