

## Sleep-Disordered Breathing and Chronic Opioid Therapy

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### 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.

*Setting.* A private clinic specializing in the treatment of chronic pain.

*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 ( $\geq 5$  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; Chronic 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 nonmalignant 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 mainte-

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nance 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-released 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. Air-

flow 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  $\geq 5$  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/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  $\geq 5$  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  $< 30$

**Table 1** Medication usage of the patients expressed as percentage of the sample ( $n = 140$ )

Medication	Mean	95% CI
Methadone and other opioids	29	22–27
Methadone as sole opioid	4	2–9
Benzodiazepines	36	28–44
Antidepressants	36	28–44
Anticonvulsants	34	26–42
Nonsteroidal analgesics	11	6–16
Muscle relaxants	28	20–34
Stimulants	16	10–22
Antihistaminics	4	2–9
Proton pump inhibitors	8	4–14

events per hour; and severe apnea–hypopnea index  $\geq 30$  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 oxycodone (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 morphine and diazepam equivalents were transformed logarithmically ( $\log_{10}([x + 1])$ ) 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 determine 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 correlation coefficients.

Statistical analyses were conducted using Splus version 7.0 (Insightful Corp, Seattle, WA). Confidence 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/m<sup>2</sup>. The female-to-male ratio was 1.51 to 1. The most common reason for around-the-clock opioid therapy 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 analgesics, benzodiazepines, antidepressants, muscle relaxants, anticonvulsants, stimulants, antihistaminics, 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 sleep apnea, and 8% had both central and obstructive

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

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

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

Variable	Apnea–hypopnea index			Central apnea index		
	Coefficient	SE	P value	Coefficient	SE	P value
Age	−0.001	0.004	0.790	−0.004	0.005	0.430
Gender	−0.055	0.051	0.281	0.046	0.057	0.422
Body mass index	0.014	0.007	0.045*	0.000	0.008	0.971
Antidepressants	0.075	0.052	0.152	0.036	0.057	0.537
Nonsteroidal analgesics	0.042	0.075	0.571	0.044	0.083	0.598
Muscle relaxants	−0.118	0.055	0.034*	−0.105	0.061	0.087
Anticonvulsants	0.081	0.051	0.116	0.039	0.057	0.493
Antihistaminics	−0.107	0.147	0.467	−0.200	0.163	0.223
Stimulants	0.006	0.065	0.925	0.037	0.072	0.607
Proton pump inhibitors	−0.046	0.088	0.603	−0.148	0.098	0.133
Methadone	0.139	0.051	0.007*	0.164	0.056	0.004*
Benzodiazepines	0.044	0.050	0.376	0.114	0.055	0.042*

\*  $P < 0.05$ .

Age (years) and body mass index ( $\text{kg}/\text{m}^2$ ) 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.

tive 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).

**Table 4** Dose–response relations between opioids, benzodiazepines, and the indices of sleep apnea: multivariable models

Variable	Apnea–hypopnea index			Central apnea index		
	Coefficient	SE	P value	Coefficient	SE	P value
Age	0.000	0.004	0.998	−0.002	0.004	0.636
Gender	−0.065	0.049	0.186	0.026	0.054	0.631
Body mass index	0.013	0.007	0.069	−0.003	0.008	0.743
Benzodiazepines	0.107	0.077	0.166	0.247	0.084	0.004*
Methadone	0.138	0.044	0.002*	0.130	0.049	0.008*
Nonmethadone opioids	0.113	0.076	0.140	0.073	0.083	0.385
Muscle relaxants	−0.109	0.054	0.046*	−0.104	0.059	0.081

\*  $P < 0.05$ .

Age (years) and body mass index ( $\text{kg}/\text{m}^2$ ) 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).

## 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 underdiagnosed 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 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 ret-

rospective 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.

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## 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

Opioid	Multiplier for equivalent oral morphine dose (mg)	Opioid	Multiplier for equivalent oral morphine dose (mg)
Oxycodone*	1	Codeine*	0.15
Hydrocodone*	1	Propoxyphene**	0.2
Hydromorphone*	4	Buprenorphine††	50
Methadone (Chronic)*	3.75	Tramadol††	0.2
Fentanyl (Transdermal)†	20.8	Butorphanol**	5
Fentanyl (Oral)†	37.5	Morphine (Intravenous)¶	3
Levorphanol§	30		

\* Calculated using <http://www.globalrph.com/narcoticonv.htm>

† *Clinical Pulmonary Medicine* 2002; 9(3): 157–163.

‡ MD Anderson hospital recommendation, see link [http://utmext01a.mdacc.tmc.edu/mda/cm/CWTGuide.nsf/0/146c6ff7a8a4352f8625685d00745c26/\\$FILE/Ca%20Pain%20V4%20group.pdf](http://utmext01a.mdacc.tmc.edu/mda/cm/CWTGuide.nsf/0/146c6ff7a8a4352f8625685d00745c26/$FILE/Ca%20Pain%20V4%20group.pdf)

§ <http://www.ohsu.edu/ahec/pain/part2sect6.pdf>

¶ *Cancer Control* 2000; 132–141.

\*\* Canadian Pharmacists Association. *Compendium of Pharmaceuticals and Specialties*. 35th ed. Ottawa: Canadian Pharmacists Association, 2000:980.

†† Twycross R, Wilcock A, Charlesworth S, Dickman A. *Palliative Care Formulary*. 2nd ed. London: Radcliffe Medical Press Ltd., 2002:171.

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.

**Table A2** Calculation of diazepam equivalents

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

Source: <http://www.benzo.org.uk/manual/bzcha01.htm#24>