The Relationship among Chronic Pain, Opiates, and Sleep

By

Carla R. Jungquist

Submitted in Partial Fulfillment

of the

Requirements for the Degree

Doctorate of Philosophy

Supervised by

Professor Jeanne Grace

School of Nursing

University of Rochester

Rochester, NY

2008

Curriculum Vitae

The author was born in Elmira, New York on August 25, 1958. She received a diploma in registered nursing from the Arnot Odgen School of Nursing in Elmira, N.Y., 1981. She then attended the State University of New York in Brockport, N.Y., receiving her Bachelors in Nursing in 1990. In 1995 she graduated from the University of Rochester, School of Nursing, with a Masters in Nursing, certifying as a Family Nurse Practitioner. While attending her Master's program she received a primary care core scholarship from the State of New York. At graduation she was the recipient of the Elizabeth Clinger Young Award for most exemplifying the qualities of great compassion, courage and concern for others. The award was presented by the faculty of University of Rochester, School of Nursing.

While attending college, she worked part time in the area of critical care nursing from 1981 to 1990 and home health nursing between 1990 and 1996. While working in home care nursing she provided care for hospice patients and patients living with HIV/AIDS. After graduating from her Nurse Practitioner program, she assumed the position of Nurse Practitioner and Medical Department Supervisor at an inner city addiction treatment program. There she cared for mostly homeless and uninsured patients suffering from addiction and mental illness. In 1999 she accepted a position as Nurse Practitioner at the University of Rochester Pain and Symptom Management Center.

After the Pain Center closed at the end of 2000, she started working per diem at the Sleep Research Laboratory in the University of Rochester. There she became acquainted with the director of the lab, Dr. Michael Perlis, who has served as a dedicated mentor, introducing her to research and encouraging her through her doctoral studies. In

2001, she accepted a position at the Canandaigua Veterans Administration Medical Center (VAMC). In this newly developed position, she started a pain initiative in the inpatient facilities and opened a nurse practitioner run pain clinic caring for veterans of all ages. In 2003 she received the Department of Veterans Affairs Secretary's Award for Excellence in Nursing awarded to an Advanced Practice Nurse, Upstate New York.

While working at the VAMC she continued to conduct research with Dr. Perlis. In 2004 she was co-investigator on a R-21 NIH grant by the National Institute for Nursing Research to study Cognitive Behavioral Therapy for Insomnia in Chronic Pain patients. After encouragement by her mentor and the program officer at NIH, Dr. Kathy Keopke, she applied and was accepted into the doctoral program at the University of Rochester, School of Nursing. She continued her involvement in research while attending graduate school.

As project director she was responsible for all aspects of the study and managed the data with the oversight of the data management team in the SON research center. In fall 2006 she received a scholarship from the Graduate Assistance in Areas of National Need Scholarship Grant at the University of Rochester to continue as a full time student while she worked on her dissertation. While writing her dissertation, she also worked with statistician, Xin Tu, on analyzing the results and with Dr. Perlis writing the manuscripts for the NIH funded study. She currently has two first authored manuscripts submitted for publication and has presented her research at the Associated Professional Sleep Societies, American Society for Pain Management Nursing, and the Eastern Research Nurses Society annual conferences.

Acknowledgments

Growing a seasoned nurse into a nurse researcher takes a community effort. I would like to acknowledge those who contributed to my professional achievements and ability to perform this dissertation study.

First, I want to thank my children for sharing me with my career and scholarly endeavors. My love, Gary, for all the support, emotional and financial, but mostly for keeping life in perspective with the use of humor.

Second, Dr. Perlis, for your mentorship, shared authorship, encouragement when I was having a meltdown and most of all for your friendship. You are truly a giving mentor.

Third, to Dr. Brydon Grant, Dr. Don Greenblatt, Dr. Joseph Modrak, Dr. Michael Yurcheson, and Dr. Robert Israel, the sleep medicine physicians and their staff who supported me with recruitment and data collection for this study.

To all the dedicated faculty and staff at the School of Nursing especially Dr. Harriet Kitzman and her data management team; and Dr. Maggie Kearney for her dedicated leadership and "mothering" qualities.

I want to thank the members of my dissertation committee, Dr. Grace, Dr Flannery and Dr. Perlis. Dr. Grace, you have been my professional idol since my Master's program. Thank you for getting me through!

And finally, for my patients living with chronic pain who have inspired my research from a desire to provide them with the safest care possible.

Abstract

Purpose

The overall aim of this study was to examine the relationships among chronic pain, opiates, respiration, and sleep in a sample of subjects referred for assessment of sleep disorders. This study assessed: (a) whether increasing dosages of opiate predict severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities, and/or excessive daytime sleepiness; (b) whether the study groups ([no pain vs. pain] and [pain minus opiate treatment vs. pain plus opiate treatment]) differed with respect to severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities; (c) whether the known risk factors for sleep disordered breathing differed for persons with and without chronic pain, and (d) whether intensity of pain predicted severity of sleep disordered breathing.

Methods

A descriptive cross sectional study was conducted. There were two types of independent variables, (a) risk factors for sleep disordered breathing (BMI, age, gender, number of systems affected by co-morbid diseases, and presence of anatomical abnormalities typical of obstructive sleep apnea), and (b) those that were directly related to the investigational hypothesis (pain incidence and intensity and/or opiate use and dose). Dependent Variables included: measures of sleep disordered breathing (e.g., frequency of central and obstructive events), sleep architecture (e.g., percent of stages 1-4 and REM), and sleep continuity measures (e.g., Sleep Latency, Number of Awakenings, and Total Sleep Time). After orthogonally coding for group membership, regression models were used for statistical analysis.

Results

Data was collected on a total of 419 subjects (no pain [n = 171], pain –opiate Tx [n = 187], and pain +opiate Tx [n = 61]). Sample demographic (mean +/- SD) was as follows: age 50 yr ± 12.; 51% male; BMI 33.8 ± 7; Epworth Sleepiness Scale 10.3 ± 5; pain intensity 3.8 ± 2 (0-10 scale); morphine equivalent dose 152 ± 195 mg; and 98% of subjects with pain had non-malignant chronic pain. Per study hypotheses (a) there was a positive dose response relationship between amount of opiate and frequency of central apneic events and percent of stage 3/4 sleep; (b) the [no pain vs. pain] group comparison revealed that subjects with pain had a lower percent of stage 1 sleep, and the [pain minus opiate vs. pain plus opiate]) group comparison revealed that subjects treated with opiates had significantly more central apneic events, more stage 2 sleep and less REM sleep; (c) the known risk factors for sleep disordered breathing differ in persons with and without chronic pain (chronic pain subjects were older, female and suffered from more comorbidity); (d) there was a relationship between pain intensity and frequency of central apneic events and obstructive apneic events. Greater pain intensity was associated with more frequent central apneic events and fewer obstructive apneic events.

Conclusion

These data suggest that the management of chronic pain with opiates is not likely to exacerbate obstructive sleep apnea at stable opiate doses; however; central sleep apnea may be worsened. The magnitude of the effect is modest, and the clinical relevance of the effect is unknown. Thus, the potential for marginal respiratory disturbance (an increase of 2.8 central events for every 100 mg. morphine equivalent opiate dose) must be weighed against the therapeutic value of pain management with opiates.

Table of Contents

Curriculum Vitae ii
Acknowledgments..... iv
List of Tables viii
List of Figures..... ix
Chapter 1: Background and Significance 1
Chapter 2 – Review of the Literature..... 7
Chapter 3: Methods..... 58
Chapter 4: Results..... 84
Chapter 5: Discussion 110
References..... 120

List of Tables

Table 1. Avg. Gr. of Opiates Dispensed Annually Per Retail Pharmacy in the U. S. Comparing 1997 to 2005 12

Table 2. Chemical Classes of Opiates.....15

Table 3. Oral Opiate Equivalent Doses.....18

Table 4. Fentanyl to Morphine Equivalent Dose 19

Table 5. Methadone to Morphine Equivalent Doses 20

Table 6. Effects of Opiates on Percentage of Sleep Stages in Absence of Pain 44

Table 7. Efficacy Trials of opiates and Measures of Sleep Continuity 48

Table 8. Operationalization of Study Variables.....66

Table 9. Medical Diseases Associated with Sleep Disorders, Categorized by System 69

Table 10. Analysis Strategy 82

Table 11. Type and Number of Polysomnography Procedures Per Site for Study Period 86

Table 12. Sample Characteristics By Site.....88

Table 13. Means of Sleep Variables by Group 89

Table 14. Other Medication Use.....90

Table 15. Regression Coefficients for Dependent Variable Percent of Stage 3/4 Sleep94

Table 16. Coding for Vectors.....96

Table 17. Descriptive Statistics for Risk Factors by Group.....102

Table 18. Significant Predictors for Higher Level on Dependent Variables 109

List of Figures

Figure 1. Diagram of group assignment for hypothesis.....61

Figure 2. Sample size estimates from feasibility pilot study at site A.....63

Figure 3. Sample size projected from the feasibility study.....63

Figure 4. Examples of pain assessment scales.....73

List of Appendices

Appendix A. Sleep Disorders Questionnaire (Site A & B) 151

Appendix B. Sleep Disorders Questionnaire (Site C).....154

Appendix C. Brochure for Site B.....162

Appendix D. Letter of Introduction to Study for Potential Subjects 163

Appendix E. Data Collection Instrument.....164

Appendix F. Informed Consent (site A) 168

Appendix G. Informed consent (site B).....171

Chapter 1: Background and Significance

Chronic non-malignant pain is a debilitating condition that is associated with negative health outcomes such as obesity, depression, and disability and affects approximately 30 million adults in the United States (American Pain Foundation, 2005; Center for Disease Control, 2007; National Center for Health Statistics, 2006). The cost to society is as much as $225.8 billion a year (Stewart, Ricci, Chee, & Morganstein, 2003).

In an effort to address the suffering and improve the quality of life and functioning of patients experiencing chronic non-malignant pain, professional organizations such as the American Pain Society, International Association for the Study of Pain, American Geriatrics Society, American Society for Pain Management Nurses, and National Institutes of Health now advocate for the use of opiate medications for moderate to severe uncontrolled pain that is refractory to other forms of therapy (American Geriatrics Society, 2002; American Pain Society, 2002; Joranson & Gilson, 2006; The Open Mind Initiative, 2006). Subsequent to this initiative, the average grams of opiate medications purchased per retail pharmacy has increased more than 300% from 1995 to 2003 (United States Department of Justice Drug Enforcement Administration, 2006).

The long term use of opiates for the management of chronic non-malignant pain is controversial among both providers and experts in the field. There is substantial literature that supports the use of opiates for acute and cancer pain management. Current evidence for long-term use for chronic non-malignant pain is sparse and does not provide a convincing argument that long term opiate use is safe or that it increases quality of life and functioning of patients (Eisenberg, McNicol, & Carr, 2005; Moore & McQuay,

2005). Health care professionals continue to argue the balance of risks and benefits of using opiates for the management of chronic pain while feeling pressured by threats of law suits and reprimands from governing bodies such as the Joint Commission for Accreditation of Healthcare Organizations, the Department of Health, or the Drug Enforcement Agency for either over prescribing opiates or not managing pain adequately. Potential risks when using opiates include adverse effects such as addiction, dry mouth, nausea, constipation, dizziness, somnolence, pruritus, vomiting, altered hormonal and immune function, decreased percentage of the stages of sleep known to be restorative, and respiratory depression during wakefulness and during sleep (Eisenberg et al., 2005; McCracken & Iverson, 2001; McNicol et al., 2003; Moore & McQuay, 2005; Wang, et al., 2005). Respiratory depression, especially as it occurs during sleep, is a major life threatening side effect that has been understudied in the context of opiate use for chronic pain management.

It is not known if the deleterious effects that opiates have on respiration and sleep when used for acute pain continue to occur when opiates are used long term in the context of chronic pain. It is possible that the deleterious effects are not a problem as adaptation occurs over time of opiate exposure. There are, however, five reports providing some preliminary evidence of potential problems. First, Farney, Walker, Cloward and Rhondeau (2003) published a case report on patients taking opiates for pain management seen in their sleep disorders clinic. On polysomnography (sleep study), three patients taking various doses of opiates exhibited respiratory disturbance that was different from the usual and was characterized by ataxic breathing, central apneic events (periods of no breath due to lack of initiation from the respiratory centers in the brain),

sustained hypoxemia and unusually prolonged obstructive hypopneas (ineffective shallow breaths due to partial obstruction of the airway and secondary to delayed arousal responses). These findings are in contrast to the usual obstructive sleep apnea found in patients of the same gender, age and body mass index.

Second, in the January 2005 issue of the Morbidity and Mortality Weekly Report (MMWR), the Center for Disease Control (CDC) reported a nearly fivefold increase in deaths from drug poisonings between 1991 and 2003. The drugs implicated were opiates prescribed for pain.

Third, results from a study of patients taking methadone long term as part of their addiction treatment program showed an association between disordered breathing during sleep and opiate use (Teichtahl, Prodromidis, Miller, Cherry, & Kronborg, 2001; Teichtahl et al., 2005; Wang, et al., 2005). In the Wang and Teichtahl studies, methadone use was found to be an independent risk factor for sleep disordered breathing in patients taking methadone in doses between 50 – 100 mg. a day as compared to controls.

The fourth publication by Walker et al. (2007) reported results from a retrospective study of 60 patients on opiates matched on gender, age and BMI to 60 patients not taking opiates. The opiate group was found to have more severe sleep disordered breathing as well as lower oxygen saturations during the day.

The fifth and most recent evidence was authored by a pain physician who sent all of his pain patients for polysomnography (Webster, Choi, Desai, Webster, & Grant, 2008). Webster et. al (2008) studied 140 pain patients, not all on opiates. They found a methadone and benzodiazepine dose relationship to severity of sleep disordered breathing, specifically central sleep apnea.

In contrast to the five reports of potential problems, in trials of the newer sustained release opiates such as Oxycontin, Opana, and Kadien, participants subjectively report improved sleep with the addition of an opiate for chronic pain (Caldwell et al., 2002; Hale, Ahdieh, Ma, Rauck, & the Oxymorphone ER Study Group 1, 2007; Rauck et al., 2006). In these studies, respiration was not objectively measured during either wake or sleep. Patients with respiratory depression during sleep, (sleep disordered breathing) usually report problems with maintaining sleep as they are awoken frequently by the hypoxemia response to initiate a breath. If opiates were causing sleep disordered breathing, it would be expected that subjective report of sleep would include sleep maintenance problems. Measuring sleep objectively via polysomnography would have provided a more precise diagnosis of the sleep outcome.

There are four possible explanations for the contrasting evidence of sleep disordered breathing in patients taking chronic opiates. Plausible explanations are (a) other risk factors for the development of sleep disordered breathing may differ between patients with and without pain, b) the body of literature in methadone maintenance patients may not generalize to chronic opiate use in the context of pain. That is, sleep disordered breathing may not occur due to the respiratory center stimulating effects from the pain, (c) the response may be opiate dose dependent, and/or (d) there may be drug differences within the class of opiate medications.

In addition to the negative impact on oxygenation from sleep disordered breathing it is plausible that by interrupting sleep opiates could be negating the normal function of sleep. Sleep is theorized to impact cognitive and memory function, mood regulation, response to traumatic injury, glucose homeostasis, and muscle restoration (Buckhalt, El-

Sheikh, & Keller, 2007; Irwin, 2002; Oginska & Pokorski, 2006; Redwine, Hauger, Gillin, & Irwin, 2000).

So the problem is the lack of direct evidence about the relationships among chronic pain, chronic opiate use and sleep disturbance including sleep disordered breathing, and the conflicting findings from the potentially relevant evidence generalized from other contexts. Additionally, the available evidence is flawed with problems relating to internal validity and generalizability. Internal validity issues include (a) case reports are informing but lack scientific rigor, and (b) subjective report of sleep is not a precise measurement of sleep architecture or respiratory status during sleep. Generalizability issues include (a) generalizing evidence in subjects without pain to patients with pain, (b) generalizing the results of opiate naive subjects to patients with long term exposure to opiates and (c) generalizing the literature on methadone to other opioids.

The unanswered questions remain (a) is there an opiate dose relationship between severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities, and/or excessive daytime sleepiness; (b) after controlling for known risk factors for sleep disordered breathing, are opiates taken for pain associated with differences in severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities, and/or excessive daytime sleepiness as compared to patients without pain or patients with pain but not taking opiates, (c) do the risk factors for sleep disturbance differ in patients experiencing chronic non-malignant pain compared to patients without chronic pain, and (d) is intensity of pain related to severity of sleep disordered breathing and/or sleep architecture?

To answer these questions, an exploratory descriptive study was conducted to examine patients being evaluated for sleep disorders to determine whether they differ on sleep parameters on the basis of chronic pain or opiate use.

Purpose of Study

This study was purposed to help build on the body of evidence in the area of long term opiate use in chronic pain patients. The results are presented to help health care providers determine (a) whether sleep disordered breathing is a problem when opiates are used long term for chronic pain, and (b) whether chronic pain patients exhibit unique patterns of sleep disturbance and sleep disordered breathing that may require unique treatment.

Chapter 2 – Review of the Literature

There are only a handful of studies and conceptual papers that address the relationships among pain, opiates and sleep. The evidence from those studies along with an overview regarding the basics of pain, opiates, sleep and respiration was used to build the theoretical and empirical foundation for the study. This chapter is structured to provide the reader with: (a) the etiology, pathophysiology and function of pain, (b) the pharmacology, indications for, and adverse effects of opiates, (c) review of the physiology and function of sleep with a particular emphasis on sleep disordered breathing, (d) physiology of normal respiration,(e) the effects of sleep on respirations, (f) the effects of pain on respirations, (g) the effects of opiates on respirations, (h) the effects of pain on sleep, (i) the effects of opiates on sleep, (j) the interaction among pain, opiates, and sleep.

Chronic Pain

Definition of Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, 1994). Pain is classified according to duration, etiology, and mechanism. Duration is divided into two categories, acute and chronic. Acute pain usually refers to a temporary state of pain regardless of etiology. Pain is classified as chronic when the duration is sustained for more than six months (International Association for the Study of Pain, 1994). Examples of etiology are accidental injury, disease related, cancer or the treatment of cancer related, and idiopathic. Pain is also further categorized by mechanism. Three common mechanisms of

pain are visceral, somatic, and neuropathic. Visceral pain originates from the organs in the thoracic and abdominal cavities. Somatic pain originates within the muscles or bones and neuropathic pain originates within the nervous system (Cherny, 2002).

Individual characteristics associated with chronic pain are age, gender, race, ethnicity and socioeconomic status. According to the National Center for Health Statistics (2006), people between 45-64 years, females, non-hispanic whites and those living below the poverty line are more likely to report having a chronically painful condition. Researchers have also found that females are more likely than males to report pain regardless of type, and cope differently with pain than males (Keefe et al., 2003; National Center for Health Statistics, 2006; Rasmussen, 1993; Y. F. Tsai, 2007; Unruh, 1996). Further studies on gender differences revealed societal expectations that males should tolerate more pain than women, thus it is more acceptable for females to access care for pain as compared to males (Pool, Schwegler, Theodore, & Fuchs, 2007).

The mechanism for the development of chronic pain is only partially understood. It is theorized that central sensitization occurs in response to repeated nerve stimulation. Central sensitization is the term that describes the neuroplasticity that occurs in the central nervous system as the result of continued messages of pain being sent from the area of injury. Neuroplasticity results in a stronger brain memory that responds more rapidly and effectively to continued nerve stimulation. The stronger memory results in lowering the pain threshold; thus the person perceives the pain as more severe than the context of the injury (Winkelstein, 2004; Woolf, 2007).

Chronic pain as compared to acute pain presents as a complex problem that affects many aspects of personhood and requires a holistic approach to treatment.

Because of the chronicity and lack of cure for the pain, persons' lives are affected physically, psychologically, socially, economically and developmentally. As a result of the multifaceted effects of living with a chronic pain condition, persons often develop co-morbid conditions such as depression, anxiety, weight gain, and physical deconditioning (Taylor et al., 2000) .

Function of Pain

It is theorized that acute pain functions as a protective mechanism. The nocioceptive system is theorized to be a conduit for input occurring from the internal and external environments of the body. The nocioceptive system senses potentially harmful stimuli in the external environment (exteroception) then communicates the danger to the brain, causing a protective behavior. If tissue is injured, the interoceptive process transmits the signal from the nocioceptors to the brain. In the case of chronic pain, the nocioceptive system is dysfunctional and the painful stimuli no longer provide a protective or meaningful function (Chapman & Okifuji, 2004; Price, Greenspan, & Dubner, 2003).

Chronic Pain and Common Co-Morbid Conditions/Characteristics

There are several co-morbid conditions and characteristics that are commonly seen in persons with chronic pain. Among them are obesity, tobacco abuse (smoking), aging, and depression (American Geriatrics Society, 2002; Lake, Power, & Cole, 2000; Leboeuf-Yde, Kyvik, & Bruun, 1999; Marcus, 2004; Ronthal, 2004; Yamakawa, Tsai, Haig, Miner, & Harris, 2004).

Obesity. Obesity is thought not only to contribute to the development of a chronic painful condition, but is also associated with increased disability related to the painful

condition. According to Leboeuf, Kyvik, & Brunn (1999), an obese person is 1.3 [99% CI (1.2-1.4)] times more likely to experience chronic back pain than a normal weight person and the more severe the obesity, the longer the duration of the pain. Additionally, patients living with pain are more likely to gain weight. In a large study Lake, Power & Cole (2000) found that over time, patients with pain gained statistically significantly more weight (7.39 kg. vs 6.29 kg.) than those without pain. Marcus (2004) studied patients referred to a chronic pain clinic. They found that controlling for pain intensity, obese (BMI $\geq$ 30) patients as compared to normal weight subjects had a higher percentage of complete disability (48.7% - 32.0% respectively), as well as significantly reduced physical functioning (63.2% - 49.1% respectively).

The evidence suggests that obesity and pain are associated. This relationship appears to be bi-directional, that is, obese persons are more likely to have a chronic pain problem, and chronic pain persons may be prone to weight gain. Obesity in pain patients is also associated with disability.

Age. According to the National Center for Health Statistics (2006) 20% of adults over the age of 65 report a persistent pain problem as opposed to 10% in the general population. In studies of painful conditions, it is has also been documented that persons over the age of 45 years are significantly more likely to report a painful condition (Chiu et al., 2006; Lacey, Lewis, & Sim, 2005; National Center for Health Statistics, 2006).

Tobacco abuse. Tobacco use is thought to contribute to the development of certain painful conditions and be associated with pain perception. Amin et al. (2007) studied smoking, cartilage loss in the knees and pain in 159 men, 19 (12%) of whom were current smokers at baseline. Amin et al. found that after controlling for age, BMI,

and baseline cartilage scores, men who smoke have greater cartilage loss and more pain than non smokers. In their study, current smokers also had higher adjusted pain scores at baseline and at follow-up than men who were not current smokers.

Smoking is also associated with perception of pain. John et al. (2006) examined the relationship between tobacco use and report of pain. They found that females with pain who smoke greater than 20 cigarettes a day were 1.6 (95% CI, 1.2–2.2) times more likely to report more locations of pain compared to females who never smoked. Milgrom-Friedman, Penman, and Meares (1983) studied pain perception in smokers, smokers deprived of a cigarette for one hour, and non smokers. They induced pain using a blood pressure cuff and monitored time to report of pain onset and length of tolerability of the pain. Deprivation of cigarettes was associated with diminished smokers' tolerability of pain significantly below that of non-smokers.

Depression. Depression is commonly seen in patients with chronic pain. It is theorized that chronic pain contributes to depression and depression contributes to chronic pain. According to Bair, Robinson, Katon and Kroenke (2003) who published a review of the literature on the relationship, 63% of persons with depression report co-morbid pain conditions and 52% of chronic pain persons referred to a pain clinic report co-morbid depression. Depression is also known to be a strong predictor for the development of back pain (Jarvik et al., 2005).

Opiates

The use of opiates has greatly increased over the past ten years. According to the United States Drug Enforcement Administration (2006) opiate dispensing by retail pharmacies has increased between 155-653 % from 1997 through 2005. See Table 1.

Table 1. Avg. Gr. of Opiates Dispensed Annually Per Retail Pharmacy in the U. S. Comparing 1997 to 2005

Opiate	1997	2005	Gram Change	% Change
Codeine	359	284	-75	-21
Oxycodone	65	489	424	653
Hydromorphone	6	14	8	126
Hydrocodone	128	399	271	211
Methadone	18	100	82	463
Morphine	87	223	136	155
Fentanyl base	1	6	5	373

(United States Department of Justice Drug Enforcement Administration, 2006)

The increased consumption of opiate medications is in large part due to a change in the standards of practice for both the management of chronic pain and addiction. In both cases the leading professional organizations now advocate for the long term use of opiates for persons whose pain or addiction is refractory to non-narcotic treatments (American Geriatrics Society, 2002; American Pain Society, 2002; Joranson & Gilson, 1998; The Open Mind Initiative, 2006). While this change represents the potential for an effective treatment strategy, it is nevertheless critical that the potential for adverse interactions be carefully delineated. The first step to better understanding potential adverse interactions is to understand the mechanism of action of an opiate.

Chemical Properties and Mechanism of Action of Opiate Medications

An *opiate* is a medication made from opium. An *opioid* is a medication or an endogenously produced peptide that acts at an opioid receptor. Opioid receptors are located throughout the body especially in the central nervous system, the autonomic nervous system and to a lesser extent on white blood cells (Jaffe & Strain, 2005).

There are four main types of opioid receptors, mu (μ), delta (δ) and kappa (κ), and the newly discovered nociceptin/orphanin FQ receptor (NOP). Recent research has also revealed that there may also be subtypes for each of the main types of receptors (Waldhoer, Bartlett, & Whistler, 2004). To produce the analgesic effect, the opiate attaches to the opioid receptor where it modulates pain by inhibiting and/or opening voltage gated calcium and/or potassium channels. Although all receptors are associated with pain control, the opiates that bind primarily to the mu receptors are known to have the strongest effectiveness for pain control. The decrease in neuronal excitability within

pathways and nuclei that are related to nocioception, translates into diminished pain sensation.

There are four main classes of opiate medications based on their chemical structure, phenanthrenes (e.g. morphines), benzomorphans (e.g. pentazocines), phenylpiperidines (e.g. meperdine) and diphenylheptanes (e.g. methadone). Within each class of opiates, the various compounds are further distinguished according to their affinity for the various types of opioid receptors (Gutstein & Akil, 2005). See Table 2.

The extent to which a compound binds to one or more receptors or receptor subtypes (selectivity and binding density) and whether it has an agonistic or antagonistic effect ultimately is responsible for therapeutic effects and adverse events. Therefore, not all opiate medications have the same actions. For example, compounds which cross the blood brain barrier, have a high affinity for the mu receptor, and act as an agonist at that receptor are more likely to produce adverse CNS effects (e.g. euphoria and respiratory depression). One example of such a compound is morphine.

Opiates also vary according to their bioavailability which results in lack of milligram to milligram equipotency/equianalgesic properties (Mercadante & Bruera, 2006; Patanwala, Duby, Waters, & Erstad, 2007; Ripamonti et al., 1998; Ripamonti, Groff et al., 1998). For example, the bioavailability of oral morphine ranges between 15 – 65%, hydromorphone 29 – 95%, and methadone 67 – 91%. Bioavailability depends on chemical structure, formulation of the pill, active metabolites, first-pass metabolism by the liver and individual differences in absorption by the gastrointestinal (GI) tract. Differences in absorption could be related to diseases of the GI tract and/or co-administration of medications that affect gastric pH and absorption of the opiate.

Table 2. Chemical Classes of Opiates

Phenanthrenes	Benzomorphans	Phenylpiperidines	Diphenylheptanes
morphine*	pentazocine	meperidine*	methadone*
codeine*	diphenoxylate	fentanyl*	propoxyphene*
hydrocodone*	loperamide	sufentanil*	
hydromorphone*	alfentanil	remfentanyl*	
levorphanol*			
oxycodone*			
oxymorphone*			
buprenorphine			
nalbuphine			
butorphanol			
naloxone			
heroin*			

(Thomson Healthcare, 2007)

Note. * highest affinity for and is an agonist at the mu opioid receptor.

It is not known whether opiates that have their primary effect as agonist on the mu receptor differ as to the extent or intensity of adverse effects. There has been one study examining whether there were differences between morphine and oxycodone on their ability to influence ventilatory responses under conditions of imposed hypercapnia and hypoxemia in healthy individuals. The investigator showed there are no differences in ventilatory effects between intravenously given morphine 15 mg, oxycodone 15 mg. and the combination of both as compared to placebo (Ladd et al., 2005).

Equianalgesic Opiate Dose

Due to the differences in bioavailability among the various opiates, tables of equianalgesic doses have been developed for use by researchers and clinicians. The tables are used during clinical trials of head to head efficacy comparisons of opiates as well as for opiate conversions in the clinical setting. The equianalgesic dose ratios were developed using anecdotal data as well as data derived from single dose study designs. Both of those techniques lacked scientific rigor for investigating comparisons between opiates. More recent versions of the conversion tables have been developed from opioid conversion studies conducted previously in cancer patients. These studies entail higher levels of scientific methodology but findings are not consistent. The inconsistency is blamed on the difficulty in measuring pain as well as individual differences in absorption of the various opiates. Developers of the equianalgesic dose ratios accept the limitations of their research, and publish the tables with warnings that conversions based solely on opiate conversion tables are over simplifications of pain management. Individual differences are likely to occur and present with potential adverse consequences

(Mercadante & Bruera, 2006; Patanwala et al., 2007; Ripamonti, Groff et al., 1998). See Tables 3, 4, & 5.

Potential Adverse Effects from Opiates

There are a variety of adverse events associated with the use of opiates that occur within the cardiovascular, gastrointestinal, neurological, endocrine, and respiratory systems. The most common adverse effects are constipation, dizziness, drowsiness, dry mouth, pruritus, headache, nausea, vomiting and respiratory depression (Cowan et al., 2005; McNicol et al., 2003; Rauck et al., 2006; Rauck et al., 2007).

Table 3. Oral Opiate Equivalent Doses.

Medication	Oral dose
morphine	30mg
oxycodone	20mg
hydromorphone	7.5mg
meperidine	300mg
codeine	200mg
hydrocodone	30mg
propoxyohene HCL	130mg
propoxyphene napsylate	200mg

Note. From *Principles and Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (p. 14-15), by American Pain Society, 1999. Glenview, IL.

Table 4. Fentanyl to Morphine Equivalent Dose

Fentanyl	Morphine
12 mcq/hr	45mg
25 mcq/hr	90mg
50 mcq/hr	180 mg
100 mcg/hr	360 mg

Note. From *Principles and Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (p. 14-15), by American Pain Society, 1999. Glenview, IL.

Table 5. Methadone to Morphine Equivalent Doses

Methadone	morphine to methadone ratio
<30mg	2:1
31-99mg	4:1
100-299mg	8:1
300-499mg	12:1
500-999mg	15:1
1000-1200mg	20:1

Note. Adopted from "The rediscovery of methadone for cancer pain management" by Ayonrinde & Bridge, 2000, in *the Medical Journal of Australia,* 173, p. 536. Adapted with permission of the author.

Sleep

Definition of Sleep

Sleep is "a natural periodic state of rest for the mind and body, in which the eyes usually close and consciousness is completely or partially lost, so that there is a decrease in bodily movement and responsiveness to external stimuli" (Pickett, 2000). An adult between the ages of 25 and 65 usually sleeps between 7.5 and 8 hours without prolonged waking during the period of 11 PM to 8 AM. With aging, total sleep time in adults decreases by about ten minutes per decade (Ohayon & Lemoine, 2004; Ohayon, 2004). Sleep usually occurs within 30 minutes of intention and adults usually express the feeling of being energetic and rested on waking in the morning. With normal sleep, there is a denial of any need, desire, or propensity to sleep during the day. During observation of the sleep period, the body is lying down with limited movement, the eyes are closed and respiration may be slow and shallow or erratic according to what phase of sleep the person is in. Although sleep appears to be a single behavior, it actually represents a cycling through a defined set of brain activity states. These states are labeled by stages according to the frequency and amplitude of electroencephalographic (EEG) waveforms. There are two phases of sleep, Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM). Within NREM sleep, there are four stages (stage 1, 2, 3, 4).

The procedure used to objectively measure sleep is called polysomnography (PSG). During the PSG procedure several physiologic variables are measured and recorded during sleep. Physiologic sensors are placed on the head, face, chest, and legs to measure: (a) brain electrical activity (electroencephalogram), (b) eye and jaw muscle movement (electrooculogram, electromyogram), (c) leg muscle movement

(electromyogram), (d) nasal airflow,(e) respiratory effort (chest belts), (f) cardiac rate and rhythm (electrocardiogram), and (g) vascular oxygenation (peripheral oxygen saturation). The data derived from PSG is collectively used to determine sleep continuity, sleep architecture, and sleep disordered breathing (Kushida et al., 2005).

Sleep continuity is the collective term used to describe (a) minutes to get to sleep (sleep latency), (b) total minutes asleep (total sleep time), (c) minutes awake after the onset of sleep (wake after sleep onset), (d) minutes awake before the planned wake time (early morning awakenings), and (e) percentage of time asleep as compared to time in bed (sleep efficiency). *Sleep architecture* is the term used to describe (a) total minutes of stage 1, 2, 3/4, and REM sleep, and (b) percentage of sleep time spent in each phase and stage of sleep. *Sleep disordered breathing* is the term used to describe impaired respiratory status during sleep (Mitler, Poceta, & Bigby, 1999).

As mentioned previously, sleep is not just a single behavior. Sleep represents a cycling of brain activity that is closely correlated with cycling of cardiac and respiratory activity (see section on sleep and respiration). During sleep, brain waves transition from low frequency, high amplitude (alpha, beta and gamma) bands to high frequency low amplitude (theta and delta) bands. The stages of sleep reflect the various frequency bands.

Stage one is the stage of transition between wakefulness and sleep. There is low voltage and mixed frequency (2-7 Hz) of EEG activity without any evidence of REM. In adults, percentage of stage one ranges between 1 – 5% (Mitler et al., 1999). See appendix A for examples of sleep stages.

Adults usually spend 15 – 20% of their sleep time in stage two. This stage is represented on EEG by relatively low voltage and mixed frequency (2-7 Hz) with sleep spindles (12-14 Hz activity for at least 0.5 seconds) and K complexes (triphasic potentials with negative sharp waves followed by positive component lasting >0.5 seconds).

Stages 3 and 4 sleep are very similar in character, usually scored together on PSG, and collectively are called *slow wave sleep*. Normal percentage of slow wave sleep is between 5-13 percent (Carskadon & Dement, 2005). Delta waveforms (2 Hz or slower frequency with amplitude of 75 μVolts from peak to peak) are characteristic of this stage of sleep. When delta waveforms occur 20-50% of the time the stage is labeled as stage 3, when they occur more than 50% of the epoch being examined, the stage is labeled as 4 (Mitler et al., 1999).

Rapid Eye Movement (REM) sleep is known for the period when most dreaming occurs. The first phase of REM usually occurs after about 80-100 minutes of sleep (Carskadon & Dement, 2005). During REM sleep EEG activity is low voltage and mixed frequency with characteristic bursts of saw tooth waveforms. Also unique to REM, skeletal muscle tone is at a minimum and eye movements are frequent and brisk.

There are several theories about the function of sleep. Generally it is thought that sleep functions to (a) restore body tissue (NREM) and brain tissue (REM), (b) conserve energy (NREM and REM), (c) reinforce memory (REM), (d) maintain motor (REM) and nonmotor (NREM) circuitry, and (e) regulate body temperature (Chokroverty, 1999).

Common Disorders of Sleep

Insomnia, sleep disordered breathing, and restless leg syndrome are the most common sleep disorders. According to the 2005 Sleep in America poll twenty-one

percent of the population think they have a sleep disorder (Hiestand, Britz, Goldman, & Phillips, 2006).

Insomnia. It is estimated that at any one point in time about 9% of the population meet the diagnostic criteria for insomnia (Hiestand et al., 2006). Insomnia is defined as difficulty initiating sleep (sleep latency), difficulty staying asleep (sleep maintenance), waking before planned wake time (early morning awakenings) and/or complaints of sleep that is chronically non-restorative or of poor quality (Lineberger, Carney, Edinger, & Means, 2006). In addition to the assessment of night time sequelae, it is helpful to assess the extent of daytime fatigue and or sleepiness. Patients with insomnia are more likely to report daytime fatigue as opposed to excessive daytime sleepiness. Fatigue and sleepiness differ as with fatigue, patients are unlikely to be able to nap.

Although some people have an innate propensity for the development of insomnia, there is usually some event that precipitates an acute period of poor sleep. The event could include birth of a child, death of a loved one, loss of a job, and/or the development of an acute or chronic medical condition. Poor adaptation to the stress of the event and to the insomnia itself can result in the development of chronic insomnia.

Chronic insomnia is best treated with cognitive behavioral therapy for insomnia (CBT-I) including the combination of sleep restriction, stimulus control, sleep hygiene, cognitive therapy, and relaxation exercises. Insomnia is also effectively treated using medications although CBT-I offers better long term gains not seen with medication use (Smith et al., 2002).

Sleep Disordered Breathing (SDB). Sleep Disordered Breathing is an encompassing term that includes obstructive sleep apnea, central sleep apnea, and upper

airway resistance syndrome. Prevalence of obstructive sleep apnea is estimated to range between 7 – 14% in males and 2 – 7% in females (Young & Peppard, 2005). Obstructive sleep apnea (OSA) disorder is characterized by recurrent absence of breath for periods of ≥ 10 seconds due to collapse of the lower posterior pharynx. Central sleep apnea (CSA) disorder is the repeated absence of breath for periods of ≥ 10 seconds due to the temporary loss of ventilatory effort (White, 2005). Upper airway resistance syndrome is the term used for a lesser form of OSA where only partial airway collapse occurs.

Sleep apnea is measured using polysomnography and is reported as the average number of apneic/hypopneic events (central and/or obstructive type) per hour on average over the night and is called the apnea hypopnea index (AHI). Some patients exhibit the combination of an obstructive apneic event and central apnea event at the same time. If this occurs, the event is labeled mixed apnea event. Clinically, mixed apnea events are usually considered obstructive in nature. Mixed apnea events are added into the AHI. An AHI of ≥15 with complaints of excessive daytime sleepiness is considered clinically significant, requiring treatment.

Although polysomnography is needed to diagnose SDB, there is some evidence that subjective screening for sleep apnea is correlated with polysomnography findings (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). Examples of screening questions are (a) do you wake gasping for breath, (b) has your bed partner witnessed apneic events, (c) do you suffer from excessive daytime sleepiness, and (d) do you snore. According to Netzer et al. (1999) subjective report screening for sleep apnea is 0.62 sensitive and 0.43 specific for AHI of >10.

Predictors of OSA include obesity, male gender, snoring, witnessed apneas, excessive daytime sleepiness and hypertension (Flemons, Whitelaw, Brant, & Remmers, 1994; Guilleminault & Bassiri, 2005; Young, Peppard, & Gottlieb, 2002). Physical anomalies that increase the likelihood of having OSA are cricomental space of 1.5 cm or less, pharyngeal grade of more than II, and the presence of an overbite (W. H. Tsai et al., 2003). The diagnosis and treatment of OSA is important to prevent hypertension, cardiovascular morbidity or mortality, sleepiness, impaired cognitive function, decreased quality of life, and motor vehicle accidents (Young et al., 2002).

Risk factors for the development of central sleep apnea include medical conditions that affect the cardiac and respiratory systems, medications/drugs that depress the central nervous system and age >65 years. Additionally, central apnea events may occur as the result of hypoxia occurring from OSA and represent as either central apneic events or mixed apnea events (White, 2005).

Treatments for obstructive sleep apnea include continuous or bi-level positive airway pressure (CPAP/bi-PAP), oral pharyngeal surgery, oral appliances affecting tongue placement, or weight loss. Treatment for central sleep apnea is usually directed at the cause of the apnea. For example, oxygen therapy for patients with obstructive lung disease, the addition of agents to improve cardiac output in patients with cardiac disease, or the weaning down of medications that may be inducing the central apneic events. In general, is it thought that CSA events are less likely to be associated with oxygen desaturations, and most times disappear when the obstructive apnea and subsequent intermittent hypoxia is treated. Less if known about the clinical relevance of CSA in absence of OSA.

Restless Leg Syndrome (RLS). Restless Leg Syndrome is a sleep disorder thought to be the result of alteration in the dopamine system. During sleep, the symptoms of RLS are Periodic Leg Movements of Sleep (PLMS). The movement can be associated with arousals from sleep. The criteria for the formal diagnosis of RLS includes PLMS found on PSG with daytime complaints of uncomfortable sensations in the legs alleviated only by walking or leg movement. Periodic limb movements of sleep in isolation from daytime complaints are associated with aging, depression, spinal cord damage, peripheral vascular disease, and mineral and electrolyte imbalance (Montplaisir, Allen, Walters, & Ferini-Strambi, 2005).

Common Co-morbidities found with Sleep Disorders

As mentioned above, there are certain diseases that predispose to the development of a sleep problem. Examples of these are cardiovascular disease (stroke) and congestive heart failure predisposing to central sleep apnea; Parkinson's disease and spinal cord damage predisposing to periodic limb movements of sleep/RLS; obesity and congenital anomalies of the upper respiratory tract predisposing to obstructive sleep apnea; and depression predisposing to insomnia (Sanders, 2005). Some of these co-morbidities such as cardiovascular disease and obesity may also have a reciprocal relationship with sleep disorders. Specifically, certain types of sleep disorders may contribute to the development of cardiovascular disease, diabetes, depression and obesity (Alajmi et al., 2007; Budhiraja, Sharief, & Quan, 2005; Hargens, Nickols-Richardson, Gregg, Zedalis, & Herbert, 2006; Ryan, Taylor, & McNicholas, 2005; Yee, Liu, Phillips, & Grunstein, 2004). Following is the evidence of how sleep disturbance *may* contribute to the development or progression of co-morbidities.

Cardiovascular Disease (CVD). Sleep disordered breathing is associated with negative health consequences that go beyond disturbed sleep. As a surrogate marker of cardiovascular disease, hypertension is commonly used as an outcome measure in research. Peppard, Young, Palta and Skatrud (2000) prospectively investigated the association between SDB and hypertension. The Wisconsin sleep cohort study followed 709 subjects for up to eight years. They found that after controlling for age, gender, alcohol use, body habitus, and baseline blood pressure subjects with an AHI of >15 were 2.89 (95% CI, 1.46 – 5.64) times more likely to develop hypertension than subjects with AHI <15.

Theorized mechanisms for the development of hypertension and cardiovascular disease in sleep disordered breathing are endothelial dysfunction, nocturnal sympathetic activation, and intermittent hypoxia. Along with hypertension, these mechanisms are likely to result in other cardiovascular complications such as coronary artery disease, heart failure, cardiac arrhythmias, stroke, metabolic abnormalities and pulmonary hypertension (Budhiraja et al., 2005). Conversely, sleep disordered breathing can occur as the result of cardiovascular disease. Cardiovascular disease which affects the respiratory center in the brain, acid base balance, and/or renal systems can result in central sleep apnea (Sanders, 2005).

Obesity. Obesity and sleep disturbance are interrelated. Sleep disorders of any type can contribute to obesity and obesity contributes to sleep apnea. In one large study, it was found short sleep (< 8 hours) was a risk factor for obesity (Moreno, Louzada, Teixeira, Borges, & Lorenzi-Filho, 2006). In another study investigating the relationship between sleep duration and type 2 diabetes mellitus (DM), Chaput, Despres, Bouchard &

Trembly (2007) found that people who sleep less than six hours were 2.09 (1.34-2.98) times more likely to have DM than people who sleep between 7-8 hours per night. Also people who sleep more than eight hours per night were 1.58 (1.13-2.31) times more likely to have DM than people who slept 7-8 hours per night. In this study, leptin levels were positively correlated ($r = 0.78$, $p. < 0.001$) with amount of body fat. Leptin is a hormone known to regulate appetite and decrease insulin levels. In obese persons, leptin resistance is thought to contribute to their obesity (Punjabi & Polotsky, 2005).

Conversely, it is thought that increased obesity contributes to obstructive sleep apnea. Newman et al. (2005) followed adults over a 5 year period. Persons with an apnea hypopnea index (AHI) of 2.0 (sd 1.4) on average at baseline increased to 6.2 (sd 7.9) on average at 5 year follow up. They found that significant predictors of higher AHI were excess body weight, central obesity, cardiovascular disease and diabetes.

Tsai et al. (2003) studied 75 patients referred to a sleep disorders center for evaluation of sleep apnea. They were on average 47.5 ± 11.65 years old and their mean body mass index was 33.1 ± 6.95 (healthy BMI 18-24). Predictors for clinically significant obstructive sleep apnea include obesity (OR 1.13, 95% CI 1.03 – 1.24), snoring (OR 12.5, 95% CI 1.42 – 110.6), hypertension (OR 10.3, 95% CI, 1.27 – 83.9), and witnessed apneas (OR 3.37, 95% CI 1.25 – 9.06). Although obesity was not the strongest predictor of sleep apnea in this study, there are studies that correlate weight loss with improved OSA as well as decrease in markers for cardiovascular disease (Dixon, Schachter, & O'Brien, 2005; Poitou et al., 2006; Strobel & Rosen, 1996).

Dixon, Schachter, & O'Brien, 2005 studied the effect of weight loss on PSG findings pre and post gastric bypass surgery. They found that after weight loss of $50.1 \pm$

15% of body weight, there was a significant decrease in apnea hypopnea index (AHI) from 61.6 $\pm$ 34 to 13.4 $\pm$ 13. Other markers of OSA were also significantly decreased such as metabolic syndrome and depression. Poitou et al. (2006) studied obese subjects, with OSA, pre and post gastric bypass surgery. They found serum amyloid A levels (marker for cardiovascular disease) to decrease by 41.7%.

There is significant evidence of the bi-directional association of obesity with sleep disruption, particularly with OSA. The mechanism of action is thought to be from endothelial inflammatory process related to intermittent hypoxia, hormone (i.e. growth hormone and leptin) imbalance and decreased activity due to sleepiness (Alam, Mahmud, Ackroyd, & Baxter, 2006). Further research in the area of weight gain from short sleep is needed to determine whether this relationship exists in sleep disturbance not caused by sleep disordered breathing.

Diabetes mellitus. Altered glucose metabolism is commonly found in patients with sleep disordered breathing but the direction of the relationship remains elusive as predisposing factors for the development of OSA and diabetes mellitus include obesity (Wild & Byrne, 2006; Young, Peppard, & Taheri, 2005). Because of this, it is difficult to know which came first, the altered glucose metabolism, obesity or OSA.

Babu, Herdegen, Fogelfeld, Shott, & Mazzone (2005) investigated the effect of treating SDB with continuous positive airway pressure on glucose levels. They found that in persons with a baseline hemoglobin A_{1C} of greater than 7% there was a significant reduction in hemoglobin A_{1C} level (9.2% $\pm$ 2.0% to 8.6% $\pm$ 1.8%). This study demonstrates that the presence of sleep disordered breathing may contribute to the development of or progression of type 2 diabetes mellitus. Similar findings have been

reported from other studies (Punjabi & Polotsky, 2005; Yee et al., 2004). Beyond sleep disordered breathing, there is some evidence that sleep continuity and architecture disruption may in itself produce metabolic changes resulting in altered glucose levels (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005; Van Cauter et al., 2007).

Depression. Depression is associated with problems of sleep initiation, sleep maintenance and early morning awakenings (Hubain, Van Veeren, Staner, Mendlewicz, & Linkowski, 1996; Hubain, Le Bon, Vandenhende, Van Wijnendaele, & Linkowski, 2006; Peterson & Benca, 2006). Persons reporting insomnia are 2 – 5.4 times more likely to develop depression (Peterson & Benca, 2006). It is also known that patients with depression take less time (62.6 $\pm$ 24 minutes) to cycle into their first phase of REM sleep, have a slightly higher percentage (24 $\pm$ 5.3) of REM and lower percentage (9.3 $\pm$ 8.4) of stage 3/4 sleep as compared to non-depressed (80 – 100 minutes, 20 - 25 %, & 20 – 25% respectively) persons (Benca, 2005; Carskadon & Dement, 2005; Peterson & Benca, 2006).

Depression is also associated with other sleep disorders such as sleep disordered breathing. Peppard, Szklo-Coxe, Hla & Young (2006) studied patients with varying degrees of SDB over a period of four years. It was found that persons with SDB have a 1.6 – 2.6 fold increased risk of developing depression. And in persons with obstructive sleep apnea, significant weight loss and improvement in AHI is associated with fewer symptoms of depression (Dixon et al., 2005).

In summary, sleep is important to maintain homeostasis and when disrupted can compromise health through various mechanisms. Sleep can be fragmented by psychological, environmental, behavioral or physiological factors. Regardless of the

factor interrupting sleep, fragmented sleep may increase the person's chance of developing cardiovascular disease, obesity, diabetes mellitus, and depression. Conversely, certain diseases such as cerebral vascular and cardiovascular disease, obesity and depression can lead to the development of sleep disturbance.

Respiration

Respiration is the act of breathing. Its purpose is to convey oxygen to tissues and cells and to dispose of the byproducts (carbon dioxide and water) of oxidation. Respiration can be assessed by measuring the depth, rhythm, and rate of breath or by measuring the consequences of respiration such as oxygen saturation and carbon dioxide levels. When investigating the effects medications have on respiration, it is important to understand the normal mechanisms of respiration.

Respiration is initiated and maintained by voluntary and involuntary stimuli. The voluntary stimulus is present during wakefulness. An example is initiating a deep breath in preparation to dive under water. The involuntary stimulus originates in the respiratory centers of the central nervous system and is regulated by chemoreceptors in the carotid and aortic bodies that respond to changing levels of oxygen and carbon dioxide within the vascular system (Fink, 1961; Hudgel, Martin, Johnson, & Hill, 1984). The ability of the central respiratory center to maintain oxygen and carbon dioxide levels depends on adequate airway patency and function of the muscles involved with the mechanical movement of the chest. The normal rate of respiration is between 8-12 breaths per minute at rest and will increase with activity. The depth of respiration depends on level of activity, age, gender, and size (Wagner & West, 2005).

Common Disorders of Respiration

Diseases of the respiratory system include asthma, emphysema, chronic bronchitis, pulmonary edema, pulmonary hypertension, pneumoconioses, and lung cancer. In addition there are diseases that have a primary effect on the neurological innervation of muscles used during respiration. Examples of such diseases are multiple sclerosis, myasthenia gravis, myotonic dystrophy and amyotrophic lateral sclerosis (Montplaisir et al., 2005).

Sleep and Respiration

During sleep, the voluntary control of respiration is absent and respiratory rate, depth and rhythm change as the brain moves through the phases and stages of sleep. During stage 1 and early stage 2 sleep, respiration rate oscillates in response to carbon dioxide and oxygen levels. In late stage 2 and in stages 3 and 4, respiratory rate and volume diminish and rhythm remains regular (Chokroverty, 1999). During all stages of NREM sleep upper airway resistance increases and motor and neuronal hypotonia occurs which diminishes the cough reflex. Chemoreceptor responses to oxygen and carbon dioxide levels remain intact. During sleep up to 25 sighs per night naturally occur and open collapsed alveoli. The sigh is usually followed by an apneic event, decreased respiratory rate or hypoventilation.

During REM sleep, respiration becomes erratic (with REM bursts) and shallow. The rate is slower than during wakefulness, rib cage response to expiration is blunted; upper airway resistance is the same or higher than NREM. Snoring (poor nasal airflow and increased upper airway resistance producing soft palate and throat vibrations) is more likely to occur during REM sleep. Additionally, chemoreceptor response to oxygen and

carbon dioxide levels is blunted. As the result of all the physiological changes that occur during sleep, respiration is the most vulnerable during REM phase of sleep (Hudgel & Devadatta, 1984).

Pain and Respiration

The presence of acute pain is known to stimulate hyperventilation as observed in the clinical setting as well as in the experiments (Glynn, Lloyd, & Folkhard, 1981). Although there have been numerous studies of respiration and pain, most are in the context of surgery and are confounded with the use of anesthetic and opiate medications. There are two experimental studies demonstrating that induced pain may decrease the respiratory depressive effects of opiates (Borgbjerg, Nielsen, & Franks, 1996; Karan, Voter, Palmer, & Ward, 2005). The evidence supports the theory that acute pain stimulates respirations, and in response to this theory, a complete set of vitals signs including respirations are measured during acute pain assessment. There is no evidence that chronic pain continues to stimulate respirations. It is generally accepted that because of physiologic adaptation to the pain, chronic pain does not significantly stimulate respirations.

Opiates and Respiration

Mu agonist opiates are thought to depress respiratory function by blunting the chemoreceptive response to carbon dioxide and oxygen, by prolonging exhalation time during wakefulness, and by increasing upper airway resistance (Fukuda, 2000; Lalley, 2003). In awake opiate naïve persons, respiratory depression with opiate exposure presents with decreased rate and depth (hypoventilation) of lung expansion (Dahan & Teppema, 2003; Dahan et al., 2004; Leino, Mildh, Lertola, Seppala, & Kirvela, 1999).

Hypoventilation impairs gas exchange resulting in increased carbon dioxide (hypercapnia) and decreased oxygen (hypoxia) and pH (respiratory acidosis). Hypoventilation can become life threatening when the oxygen level diminishes below the point where it is able to stimulate respiration. At that point respiratory arrest occurs.

Respiratory depression secondary to opiate use for acute pain has been reported numerous times in the literature and is a common concern of health care workers when administering opiates (Fukada, 2005; Winterstein, Hatton, Gonzalez-Rothi, Johns, & Segal, 2002; Winterstein, Sauer, Hepler, & Poole, 2002). Winterstein et al. (2002) found that opiates were associated with 16 percent of the preventable adverse drug reactions reported by hospitals between 1994 and 2000. The adverse drug reactions due to opiates were excessive sedation, somnolence, respiratory arrest and seizure and were associated with adverse patient outcomes such as death.

The incidence of respiratory depression in the context of long term opiate use is less well understood. In general it is thought that the respiratory depressive effect of opiates dissipates over the first few days of exposure. In a study of respiratory sensitivity and tolerance in opiate naïve rats given fentanyl, Laferriere, Colin, Durand, and Moss (2005) found that tolerance (50% recovery from initial respiratory depression) developed within 5.1 days. Specifically, rats of three age categories (pups, adults, and elderly) were given fentanyl until their minute ventilation decreased by 50%. Tolerance to respiratory depression was found to vary according to age, pups 2.6 days, adults 5.1 days, and elders 4.4 days.

Evidence in humans suggests that incomplete tolerance may occur (Athanasos et al., 2006; Stoermer et al., 2003; Teichtahl et al., 2001; Teichtahl et al., 2005; Wang, et al.,

2005). Teichtahl et al. (2005) studied ventilatory responses to hypoxia and hypercapnia in methadone maintenance patients who had been taking 50 – 120 mg of methadone for 2 – 60 months. They found that methadone patients had significantly decreased hypercapnia ventilatory response and significantly increased hypoxia ventilatory response compared to normal subjects who had been matched by age, gender, height, and body mass index. Further analysis showed respiratory outcomes were also associated with use of antidepressants. The authors theorize that these findings represent a shift in mechanism of regulation represented by a chronic reduction in ventilatory response to hypercapnia followed by a heightened response to hypoxia.

Stoermer et al. (2003) studied the safety of intravenous opioid maintenance treatment for heroin dependence. Opiate addicted subjects were randomized to either intravenous heroin or intravenous methadone in a controlled setting. They found that heroin and methadone injection in opiate dependent subjects' resulted in clinically significant respiratory depression progressing to Cheyne-Stokes pattern. Oxygen saturation decreased to 78.9 $\pm$ 8.7% and the hypoxia was accompanied with bradycardia. Respiratory depression and bradycardia was less pronounced in the methadone group as compared to the heroin group.

Athanasos et al. (2006) studied pain relief from intravenous morphine in experimentally induced pain. The subjects were 28 methadone maintenance patients on stable doses of methadone as part of their addiction treatment program. The subjects were divided into groups according to their methadone dose. While experimentally inducing pain, they were given either 15.2 mg of intravenous morphine followed by 8.3mg/hour for one hour or 2.2 mg followed by 1.2 mg. hr. as a control. Again, in opioid tolerant

methadone subjects, morphine significantly produced decreased respiration rate 12 ± 3%. The methadone subjects were found to be hyperalgesic and cross tolerant to the pain relief effects of the morphine, yet not to the respiratory depressive effects.

The evidence supports the generally accepted theory that opiates when administered to opiate naive patients can potentially produce life threatening respiratory depression. Further evidence also shows that in opioid dependent patients, intravenous delivery of morphine produces clinically relevant respiratory depression. Clinically, it is common to see patients with chronic or cancer pain on high doses of opiates who do not demonstrate overt, observable respiratory depression during wakefulness and don't die in their sleep. The question that remains is whether opiates when given long term to chronic pain patients result in respiratory depression during sleep when respirations are more vulnerable. Could it be that our patients with chronic pain taking opiates are at risk of sleep disordered breathing that could predispose them to hypertension and altered glucose metabolism? If this problem exists, further studies determining clinical relevance and appropriate treatments would be warranted.

Pain and Sleep

Sleep disturbance is common in patients experiencing pain. It is estimated that 20% of Americans complain of pain or physical discomfort that disturbs their sleep (National Sleep Foundation, 2007). Fifty nine to sixty three percent of patients referred to pain clinics report trouble initiating or maintaining sleep (Bair et al., 2003; Tang, Wright, & Salkovskis, 2007). During hospitalization, pain is the medical condition most likely to be reported as the cause of the sleep disturbance (Kuivalainen, Ryhanen, Isola, & Merilainen, 1998).

When pain is induced in the context of experimentation, the response is related to the type of painful stimuli, the location of the application, and the stage of sleep. Pain has been found to reduce the amount of stage 3/4 sleep, is more likely to cause an arousal during stage 1 and 2 sleep, and latency to nerve response is delayed in stage 3/4 and REM stages of sleep (Drewes, Nielsen, Arendt-Nielsen, Birket-Smith, & Hansen, 1997; Lavigne et al., 2000; Sandrini et al., 2001). This evidence also supports the perspective that during sleep, nocioceptive processing is occurring.

Chronic Pain and Sleep Continuity

More than half of the patients referred to chronic pain clinics report problems with initiating and maintaining sleep (Menefee, Cohen et al., 2000; Menefee, Frank et al., 2000; Morin, Gibson, & Wade, 1998; Pilowsky, Crettenden, & Townley, 1985). In studies using subjective report of sleep continuity in chronic pain patients, it has been found that there are other factors than just pain that contribute to sleep disturbance. According to Tang, Wright and Salkovskis (2007) chronic pain patients are 18 times more likely than those without pain to experience clinically defined insomnia (Insomnia Severity Index $\geq$ 15). In this study anxiety about health as well as emotional suffering as the result of living with chronic pain were the best predictors of insomnia. Menefee et al. (2000) found more severe levels of insomnia in chronic pain patients who reported less physical functioning and longer duration of pain. Pilowsky, Crettenden & Townley (1985) studied sleep, pain and mood in 100 pain clinic patients. In their sample, 70% of the subjects reported poor sleep (sleeping less than 5.3 hours per night on average). In this sample, subjects who reported poor sleep also reported clinically significant depression as compared to pain subjects who were good sleepers. It has also been found

that chronic pain patients who report sleep disturbance also report higher intensity of pain on average (Morin et al., 1998).

All of the above mentioned studies measured sleep disturbance using subjective report. The shortfall of this evidence is the lack of objective measure of the sleep disturbance. Patients with sleep disorders other than insomnia such as sleep disordered breathing and restless leg syndrome also complain of problems maintaining sleep. Therefore it is difficult to determine the true etiology of the problem without performing polysomnography.

Chronic pain contributes to sleep disturbance. It is not clear from the current evidence what type of objectively measured sleep disorder is associated with chronic pain. In addition, the biopsychosocial consequences of living with a chronic pain condition also contribute to sleep disturbance. The reverse relationship of the impact of sleep disturbance on chronic pain has also been investigated. Sleep disturbance is thought to decrease pain tolerability and pain is thought to increase sleep disturbance (Pigeon, Park, & Sateia, 2004; Raymond, Ancoli-Israel, & Choiniere, 2004; Smith & Haythornthwaite, 2004; Smith et al., 2008).

Chronic Pain and Sleep Architecture

Although there are a number of prevalence studies documenting sleep problems in chronic pain patients there are few studies that use PSG to measure sleep. Early PSG studies occurred in patients experiencing fibromyalgia. At that time, it was hypothesized that altered sleep could be the origin of the fibromyalgia symptoms. The PSG evidence revealed the occurrence of alpha (wake like) rhythms during stage 3/4 (delta) sleep (Anch, Lue, MacLean, & Moldofsky, 1991; Branco, Atalaia, & Paiva, 1994; Horne &

Shackell, 1991; Rains & Penzien, 2003; Wittig, Zorick, Blumer, Heilbronn, & Roth, 1982). The alpha waveforms were postulated to be the nocioceptive stimuli (pain) input occurring during sleep. As the evidence accumulated over time, it became apparent that alpha/delta sleep was also present in persons with other chronic pain problems (Hirsch et al., 1994).

Patients with chronic pain exhibit decreased percentage of stage 3/4 sleep (Harman et al., 2002; Nielsen, Drewes, Svendsen, Bjerregard, & Taagholt, 1994). Depending on which medications they are taking and whether they have co-morbid depression, they may also exhibit changes in REM sleep (Harman et al., 2002).

Interaction of Pain Disorders and Sleep Disorders

The discussion above has primarily focused on generalities of chronic pain and sleep. When considering individual pain conditions there are potential interactions that could occur with sleep disorders that could put the person at additive risk of negative PSG findings. Examples of this could be spinal stenosis in combination with restless leg syndrome as both of these conditions are characterized by periodic limb movements of sleep and sleep fragmentation. Another example is chronic back pain and obstructive sleep apnea as both are characterized with increase in severity of symptoms due to position during sleep. Additionally, there may be relationships between chronic pain and sleep disturbance that are specific to the disorder causing the pain. Unfortunately there are no studies in this area.

Opiates and Sleep

As mentioned previously, opiates are medications that exert their primary action on opioid receptors. There are, at minimum, 3 types of opioid receptors. The opiates'

effect is determined by which receptor they attach to and the direction of the attachment. Please refer to Table 2. Pure mu agonists such as morphine, oxycodone, fentanyl, and methadone have a higher likelihood of causing respiratory depression and are the opiates that have been most studied using polysomnography. This body of literature is studied in the context of post surgical care, methadone maintenance programs, cancer care, and more recently in the chronic pain setting. Although all the evidence is informing, each setting is confounded with its own issues. Further confounding this literature is the idea of tolerance. In order to understand the relationship between opiates and sleep in absence of pain, the literature on methadone as it is used to treat opioid addiction will be reviewed. In an attempt to address the issue of tolerance, special attention will be made to the length of time the subjects have been taking the opiate. The term *opiate naïve* will be used to connote a subject who was free of opiates before entering the research study.

Opiates and Sleep Continuity

In absence of pain, opiate naïve patients taking opiates for the purpose of research report non-restorative sleep, more awakenings, increased wake time after sleep onset, and decreased total sleep time (Kay, 1975a; Kay, Pickworth, & Neider, 1981; Lewis, Oswald, Evans, & Akindele, 1970; Pickworth, Neidert, & Kay, 1981). These studies are confounded by the subjects chosen for the study. The subjects were prisoners with a history of opiate addiction. Although they had been opiate-free for at least six months, the researchers found the subjects standing at the edge of the bed in an attempt to stay awake to enjoy the effect of the opiate. This behavior could be responsible for the findings.

Teichtahl et al. (2001) studied 22 methadone maintenance patients, comparing them to normal controls matched for age, gender and BMI. On analysis of sleep

continuity measures, they found statistically significant differences between the two groups on sleep efficiency (percentage of time asleep as compared to time in bed) and total wake time. That is, persons who were taking methadone spent more time awake in bed during the night as compared to controls. This could be explained by awakenings that occurred as the result of their hypoxemia from central sleep apneic events that were found in the methadone subjects. The evidence does not report whether arousals occurred with the apneic events. All of the methadone subjects in this study had been on stable doses for at least two months. Confounding these results is their use of other centrally acting medications such as benzodiazepines and antidepressants.

In a second study, Teichtahl et al. (2005) duplicated the results that patients taking methadone for addiction exhibit significantly more central sleep apneic events as compared to controls. But interestingly, this study did not show any statistically significant differences in sleep continuity measures. In conclusion, results of studies looking at the effects opiates have on sleep continuity have inconsistent findings. It seems plausible that the severity of apneic events also found in these studies could contribute to the sleep continuity findings.

Opiates and Sleep Architecture

Please see table 6 for unique differences in study design. Overall, this evidence shows that opiates increase stage 1 and 2 and decrease percentage of stage 3 and 4 as well as REM sleep. The clinical relevance of this information remains in question. For example, in the Dimsdale (2007) study, on the nights the subjects took morphine or methadone they received on average 19, 22 respectively minutes less stage 3/4 sleep. The health consequences of a deficit of 19-22 minutes stage 3/4 sleep is not known. It is

plausible that since stage 3/4 sleep is thought to support immune function, then receiving less than usual could put the person at risk of infection. Limitations of these studies include lack of diversity in gender, age and body mass index. Most of these studies were in young healthy non-obese males.

Table 6. Effects of Opiates on Percentage of Sleep Stages in Absence of Pain

Study	Study/Drug	Naïve	N	%stage 1	%stage 2	%stage 3-4	%REM
Lewis, et al., 1970	Heroin	yes	3	increase	ns	ns	suppresses
Kay, 1975	methadone	yes	6	Na	na	decrease	ns
Kay, et al., 1981	morphine/heroin	yes	7	Na	na	decreases	decreases
Pickworth et al, 1981	morphine/methadone	yes	13	Na	na	na	decreases
Teichtahl, et al. 2001	methadone/normal controls	no	10/19	17/7	69/57*	8/16*	17/23
Wang, et al., 2005	methadone/normal controls	no	50/20	8/10*	64/55*	15/17	15/18*
Shaw, et al., 2005	morphine	yes	7	increases	increases	decreases	decreases
Dimsdale, et al., 2007	morphine/methadone/placebo	yes	42	9/8/8	61/64/58*	8/8/12*	22/21/22

Note. na = not available; ns = not statistically significant; *statistically significant; numbers represent group mean

Opiates and Sleep Disordered Breathing

Opiates exert their actions on the respiratory system in three ways: they (a) decrease sensitivity of the peripheral and central chemoreceptors to carbon dioxide and oxygen, blunting the protective regulation of rate of respiration, (b) depress the respiratory centers in the central nervous system thus slowing respiration, and (c) decrease pharyngeal tone thus increasing the risk of upper airway collapse (Cox, 1991; Lalley, 2003; Schumacher, Basbaum, & Way, 2004).

There are three studies investigating the effect of opiates on sleep disordered breathing in subjects on long term opiate in absence of pain. Teichtahl, et al (2001) studied 10 methadone maintenance patients and 9 controls matched for age, gender and body mass index. The methadone subjects were taking between 50 -120 mg of methadone for between 2 – 60 months. Their apnea-hypopnea index ranged between 0.3 – 52.6 and consisted mostly of central apnea and hypopnea events. Only one subject was found to have an obstructive apnea index > 0. Level of significance between groups was not reported for AHI. The methadone subjects' baseline SpO2 (95 $\pm$ 1%) and sleep nadir (90 $\pm$ 4%) were significantly lower than controls.

Wang et al. (2005) studied 25 methadone maintenance subjects as compared to gender, age (35 $\pm$ 9 years), and BMI (27 $\pm$ 6) matched controls. No significant group differences were found in central apnea index (CAI), but all controls had a CAI <1 and of the methadone subjects, 30% had a CAI >5 and 20% had a CAI >10. Clinically relevant is > 5. The methadone subjects were found to have significantly more daytime sleepiness on Epworth Sleepiness Scale (7.10 $\pm$ 4.99, 2.05 $\pm$ 1.76, p = 0<

.001). Clinically relevant ESS is >10. Additionally, methadone dose was positively correlated with CAI (0.338, p = 0.023) and awake SpO2 was negatively correlated with CAI (-0.348, p = 0.021). Confounding these results is the fact that the methadone subjects were much more likely to smoke and take substances that are thought to affect respiration such as benzodiazepines and cannabinoids.

The third study recently published by Dimsdale et al. (2007) studied the effect of morphine, methadone and placebo in healthy *opiate naive* subjects. These subjects were administered either 15 mg of morphine sulfate, 5 mg of methadone or placebo just prior to sleep on three separate nights. Apnea hypopnea index was significantly different over the three nights but not clinically relevant (AHI all below 4).

The assumption that complete tolerance develops to the respiratory depressive effects of opiates may not be totally accurate. Additionally, despite opiate dependence, when subjects are given acute doses of intravenous morphine significant respiratory depression occurs. This small body of evidence is further limited by constricted generalizability to young, non-obese males. Questions remain about the influence of smoking and other medications that could potentially contribute to sleep disordered breathing in this population. Other medications include antidepressants and benzodiazepines.

Chronic Pain, Sleep and Sleep Disordered Breathing

This section will synthesize the information previously reviewed. In addition, the literature on long term use of opiates in chronic pain patients will be reviewed with special emphasis on studies measuring sleep and sleep disordered breathing.

Sleep Continuity and Opiates in the Context of Chronic Pain

This body of literature is extensive and contains efficacy and safety studies of opiates for chronic pain. See Table 7 for a summary of the pertinent studies of the most commonly used mu opiates. All the studies demonstrated the opiates' effectiveness for chronic pain management. Common themes emerged during the review that leads to the items reported in Table 7. Particularly pertinent to this study are the high attrition rates due to intolerance of side effects, and the percentage of significant somnolence reported. Other design issues limiting applicability to tolerance are the brevity of study duration and the lack of gold standard measurement of respiratory status, excessive daytime sleepiness and sleep outcomes. In general, this body of evidence represents middle age adults with chronic non-malignant pain.

Table 7. Efficacy Trials of opiates and Measures of Sleep Continuity

Author	Pain	Length	Opiate	Sample	Sleep Measure	Findings
Arkinstall et. al, 1995	chronic non-malignant	19 wk.	codeine crossover design M daily dose after titration for pain relief was 273 mg CR Codeine	n = R 46/C 30 CR M 55 yo, 56% F 0% were opiate naive	None	None % somnolence: 5% before codeine/ 16% after codeine
Caldwell et. al, 2002	osteoarthritis	4 wk.	Placebo/Morphine CR in AM/Morphine CR in PM/ Morphine IR BID P/MSCR 30mg AM/MSCR 30mg PM/MSIR 15 mg BID	n = R 295/C 184 M 62 yo, 63% female, M BMI nr, 58% were opiate naïve	Quality of sleep and use of hypnotics	Significantly improved sleep measure in all active treatment groups as compared to placebo % somnolence: 0/12/9/9

Caldwell et al, 1999	osteoarthritis	8 wk.	Placebo/Oxycodone CR/Oxycodone IR M daily dose after titration for pain relief was 40 mg.	n = R 167/C 107 M 57 yo, 63% female, M BMI 32.4	Question on pain diary "How was the quality of your sleep"?	Significantly improved sleep quality in the CR and IR groups. M group scores slightly better in CR group. % somnolence: 13/18/26
Hale et al, 2007	chronic low back pain	16 wk.	Oxymorphone CR/placebo M daily dose after titration for pain relief was 80 mg	n = R 251/C 143 M 49 yo, 53% F 0% were opiate naive	None	None % somnolence: 0/3
Kivitz et. al, 2006	osteoarthritis	2 week	Oxymorphone CR/Placebo P/10mg/40mg/50mg no titration for pain relief	n = R 370/C 198 M 62 yo, 64% female, M BMI 33.3	Chronic Pain Sleep Inventory	*improved sleep at 40 mg and 50 mg dose % somnolence: 3/9/21/19

Langford et. al, 2006	osteoarthritis	6 wk.	Placebo/Fentanyl transdermal M daily dose after titration for pain relief was 100 mcg/hr	n = R 399/C 199 M 66 yo, 65% female, M BMI nr	Question on pain diary "Pain disturbing nights rest"?	M 19.1 decrease in pain disturbing nights rest. % somnolence: 7/48
Maier et. al, 2002	Chronic non-tumor pain	2 wk.	Morphine SR/placebo M daily dose after titration for pain relief was 100 mg	n = R 49/C 48 M 49 yo, 51% female, 0% were opiate naive	VRS of Sleep quality 0 – 3 (severely disturbed)	M = 2.6 placebo M = 2.0 morphine p = <.001 % somnolence: 2/23
Markenson et. al, 2005	osteoarthritis	90 days	Oxycodone CR/Placebo M daily dose after titration for pain relief was 57 mg	n = R 109/C 36 M 63 yo, 78% female, BMI nr 40% opiate naive	Sleep Item on the Brief Pain Inventory Inference Scale	Pain interfered less with sleep = < .001 % somnolence: 5/18

Moulin et. al, 1996	chronic non-malignant pain	6 wk	Morphine SR/Benzotropine M daily dose after titration for pain relief was 83.5 mg	n = R 60/C 43 M 40 yo, 57% female, 0% were opiate naive	None	None % somnolence: 17/13
Palangio et al, 2000	chronic non-malignant pain	4 wk.	Hydrocodone 7.5mg with ibuprofen 200mg/Codeine 30mg with 30mg acetaminophen. MDD = H 25mg/H 52mg/C 102mg	n = R 469/C 333 M 51 yo, 54% female, M BMI nr 95% had previous opiate exposure	None	No sleep outcomes reported % somnolence: 44/34/37
Arkinstall et al., 1995	osteoarthritis	4 wk.	Placebo/Controlled release codeine. M daily dose after titration for pain relief was 169 mg.	n = R 107/C 66 M 62 yo, 63% F M BMI 34.2	Trouble falling to sleep? Use of hypnotics	Significantly less trouble falling to sleep and less hypnotic needed in codeine group % somnolence: 10/39

Rauck, R.L., et al., 2006	chronic low back pain	4 mo.	Morphine SR/Oxycodone CR M daily dose after titration for pain relief was morphine 86 mg and oxycodone 79.5 mg	n = R 392/C 132 M 49 yo, 61% female, M BMI 31.5	Pittsburgh Sleep Quality Index	Both opiates improved PSQI scores, morphine more so than oxycodone % somnolence: 54/60
Roth, S.H., et al., 2000	osteoarthritis	18 mo.	Oxycodone CR/Placebo P/10mg/20mg M daily dose after titration for pain relief was 39.2 mg	n = R 133/C 63 M 62 yo, 74% female, BMI nr	Quality of sleep and # of nightly awakenings due to pain	No significant differences in sleep % somnolence: 2/11/12 (wk 2)

SR=sustained release; CR = controlled release; nr = not reported; R = active treatment; C = control group

Sleep Disordered Breathing and Opiates in the Context of Chronic Pain

Respiratory depression at its worse leads to death. There is evidence of opiates being linked to unintentional deaths. In 2005 the Center for Disease Control (CDC) reported an increase in deaths from prescribed medications in the state of Utah. In review of deaths from 1991-2003 in Utah, it was found that the number of deaths from non-illicit drug poisoning from opiates had more than quadrupled (79 in 1991 to 391 in 2003) from the previous twelve years (Center for Disease Control, 2005). This fourfold change in the unintentional death rate from legal drugs was mostly due to prescribed opiates and was associated with obesity (41% of deaths had BMI >29). The obesity rate in this study is higher in comparison to the estimated obesity rate of 20-24% in Utah in 2005. Of the total 2396 unintentional deaths in Utah between 1991-2003, 1277 were from non-illicit drugs, 947 from illicit drugs and 172 from a combination of both. Alcohol was implicated in 22% of deaths and not included in above. Of the non-illicit drugs, most were opiate medications prescribed for pain. In particular, methadone deaths increased from 2 to 33 per year and most of deaths occurred in patients who had just been started on methadone. Deaths from other opiates used for pain increased from 10 to 48 per year. As sleep apnea is more likely to occur in patients who are obese, it is plausible that these deaths occurred in patients who had undiagnosed sleep apnea. It is also plausible that methadone may present with a higher risk for respiratory depression as it is clinically known to be one of the most sedating opiates.

Opiate exposure blunts the chemical control of respiration and diminishes pharyngeal tone (Dahan & Teppema, 2003; Fukuda, 2000; Romberg, Olofsen, Sarton, Teppema, & Dahan, 2003). Opiates not only depress respiratory drive, but they are

sedating. The combination of depression of respiration, the sedating effects that blunt the protective waking mechanism from sleep, and the lack of the voluntary respiratory effort can be a lethal combination. Yet in efficacy and safety trials of opiate medications, subjects report improvement in their sleep (Arkinstall et al., 1995; Caldwell et al., 2002; Hale, eet al., 2007; Kivitz, Ma, Ahdieh, & Galer, 2006; Langford, McKenna, Ratcliffe, Vojtassak, & Richarz, 2006; Maier et al., 2002; Markenson, Croft, Zhang, & Richards, 2005; Moulin et al., 1996; Palangio et al., 2000; ; Rauck, et al., 2006; Rauck et al., 2007; Roth et al., 2000). However, when sleep is measured objectively via polysomnography in methadone maintenance persons, there is some evidence that opiates actually have a negative effect on sleep quality (e.g. decrease deep sleep) and sleep disordered breathing. It is plausible that the individuals perceive they are sleeping better because of the sedative effects.

The earliest published article found addressing the possibility of sleep disturbance and/or sleep disordered breathing with opiates in persons with chronic pain was a case report by Farney, Walker, Cloward, and Rhondeau (2003). They describe three chronic pain patients who were referred to their sleep disorders center for evaluation of fragmented sleep and excessive daytime sleepiness. All three patients were found to have central sleep apnea along with the usual obstructive sleep apnea the authors expected to find. Further, the authors report the concern that traditional treatment of continuous positive airway pressure (CPAP) was not as effective in treating the person's hypoxia as in persons not on opiates. Although all three subjects were on complex medicine regimes, they did not have the traditional medical diagnoses that are associated with central sleep apnea.

Webster, et. al (2008) studied sleep disordered breathing in 140 chronic pain patients taking opiates. Patients on average were 51 years of age, with a BMI of 29.7. Seventy five percent of the subjects had an AHI of > 5. Percent of subjects with type of sleep disordered breathing was as follows: OSA 39%, CSA 24%, mixed apnea 8%, undetermined 4%. They effects coded medication classes: nonsteroidal analgesics, benzodiazepines, antidepressants, muscle relaxants, anticonvulsants, stimulants, antihistaminics, and proton pump inhibitors. They then regressed sleep measures on dose of methadone, dose of other opiates, dose of benzodiazepine controlling for age, gender, BMI and other classes of medications. They found a linear relationship between methadone dose and AHI, benzodiazepine dose and AHI, and methadone dose and CSA.

Walker et al. (2007) recently published a retrospective review of the patients referred to their sleep disorders center. They found a dose dependent relationship between chronic opioid use in pain patients and the Biot breathing patterns. Biot breathing is irregular in depth and rhythm. This study involved 60 opioid dependent chronic pain patients, matched on age, gender and BMI to 60 patients not taking opiates. It is unclear whether the control group had pain. The study participants had mean age of 52.8, were 66.7% female, and mean BMI was about 32. Patients were excluded if they had congestive heart failure, coronary artery disease, stroke, primary neurologic disease, prior use of supplemental oxygen, or had used opioids for less than six months.

The mean Epworth Sleepiness Scores (11.6 $\pm$ 5.6, 10.2 $\pm$ 5.8) were clinically significant in both groups, yet slightly higher in the opiate group. This trend was also found with all the respiratory outcome measures. The only statistically significant findings within the respiratory outcome measures were the central apnea index (12.8 $\pm$

22.4; 2.1 $\pm$ 4.1, p. <0.01), mean oxygen saturations during wake (91.0 $\pm$ 2.6; 93.1 $\pm$ 1.8, p. <0.01) and percentage of NREM sleep (89.7 $\pm$ 33.3; 91.9 $\pm$ 2.0, p < 0.01).

These investigators concluded that pain patients taking more than the morphine equivalent dose of 200 mg are at increased risk of sleep disordered breathing. There are many unanswered questions; two specifically relevant to this review are how pain severity impacted on SDB in opiate patients, and whether the risk factors for SDB in chronic pain patients differ from the usual person with SDB.

In summary, the relationship between pain, opiates, respiration and sleep has been understudied. Health care providers are forced to use the available evidence to come to ethical and logical conclusions on how best to manage chronic pain. Because of this, there are differing opinions on the use of long term opiates to treat non-malignant chronic pain. More evidence is needed to confirm causality and determine the clinical relevance of the findings.

Arguments supporting the use of opiates include trials of the newer long acting opiate medications. These studies are short term in duration of opiates use, use low doses of opiates, and don't objectively measure either sleep or respiration. Evidence against the use of opiates includes the increased death rate from prescribed opiate medications, the evidence of central sleep apnea, and the incidence of adverse effects when opiates are used for acute pain. There is also some evidence from methadone maintenance patients suggesting that complete tolerance to the respiratory effects of opiates when used for addiction may not occur. Clinicians are left to draw their own conclusions on how best to manage chronic pain patients, with or without opiate.

Plausible explanations for the conflicting evidence are (a) risk factors for the development of sleep disordered breathing may differ in patients with and without pain, (b) the body of literature in methadone maintenance patients may not generalize to chronic opiate use in the context of pain (i.e. sleep disordered breathing may not occur due to the respiratory center stimulating effects from the pain), (c) the response may be opiate dose dependent, and/or (d) there may be drug differences within the class of opiate medications. Specifically, the studies in chronic pain patients were performed on the newer long acting morphine, oxycodone, and oxymorphone formulations, not methadone.

Summary

Reviewing this body of evidence has revealed several gaps in the literature. Specifically, the evidence lacks critical elements to establish causality. There are no studies looking at a sample of chronic pain patients and prospectively following them through initiation and titration of opiate therapy for their pain. Before this type of study can be performed, pilot data are needed to establish the presence of sleep disturbance and sleep disordered breathing in chronic pain patients taking opiates. Important to establishing this relationship is to compare sleep disordered patients with and without chronic pain. So far there has not been a study involving this comparison. Further, it is important to establish whether the presence of acknowledged risk factors for sleep disturbance/sleep disordered breathing (e.g. obesity, gender, age, anatomical anomalies, and co morbidities), differ in patients with and without chronic pain. The previously mentioned studies assumed the risk factors were the same for all. Other gaps include whether severity of sleep symptoms depends on dose of opiate, intensity of pain or chemical class of opiate.

Chapter 3: Methods

Study Aims

The overall aim of this study was to examine the relationships among chronic pain, opiates, and sleep. Specifically, this study of patients referred to sleep disorders centers examined (a) whether increasing dosages of opiate predict severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities, and/or excessive daytime sleepiness; (b) whether the study groups ([no pain vs. pain] and [pain minus opiate treatment vs. pain plus opiate treatment]) differed with respect to severity of sleep disordered breathing, sleep architecture, sleep continuity abnormalities, and/or excessive daytime sleepiness; (c) whether the known risk factors for sleep disordered breathing differed for persons with and without chronic pain, and (d) whether intensity of pain predicted severity of sleep disordered breathing.

Study Hypotheses

The following hypotheses were tested:

H1: Controlling for known risk factors, higher doses of opiates would predict lower percentage of stage 3/4 and REM sleep and higher values of daytime sleepiness, obstructive apnea index (OAI) and central apnea index (CAI) and lower oxygen nadir.

H2: Controlling for known risk factors, group membership ([no pain vs. pain] and [pain minus opiate treatment vs. pain plus opiate treatment]) would be associated with differences in measures of sleep disordered breathing, sleep architecture, sleep continuity, and/or daytime sleepiness.

H3: BMI, age, gender, number of co-morbidities, and presence of anatomical abnormality are independent predictors of the likelihood that a sleep disordered person would report chronic pain.

H4: Controlling for known risk factors, higher intensity of pain would predict lower CAI, OAI, HI, higher oxygen nadir, lower excessive daytime sleepiness, higher percent of stage 3/4 and REM sleep.

Design

To address the study aims, a descriptive cross sectional study of patients referred to three sleep disorders centers was conducted. Data for this study were derived from (a) Sleep Disorders Questionnaire (SDQ) see appendices B and C, (b) the medical record and (c) reports from the PSG procedure. Prior to the start of the study, all study procedures were reviewed and approved by the University of Rochester Research Subjects Review Board (RSRB) and the human subjects review board for the participating Sleep Disorders Centers.

Sample

A sample of patients referred to three sleep disorders centers (two local and one out of state) was utilized. This sample of community based adults was chosen as they (a) provided patients both with and without a chronic pain problem for comparison purposes, and (b) were undergoing a polysomnography procedure.

Inclusion criteria were:

1. Age $\geq$ 21. Although persons of all ages are referred to the center, this study recruited/gathered data on only subjects greater than or equal to age

21. The age limitation was placed to avoid the confounding and unique sleep problems of childhood and adolescent life stages.

2. Literate in the English language. The consent and sleep disorders questionnaire were written in English.

To avoid confounding pain and sleep disorders, subjects were excluded from analysis if they had:

1. An acute pain problem. An acute pain problem (including terminal cancer pain) represents an unstable medical condition that was likely to influence sleep and confound the study findings.
2. Methadone therapy prescribed for the purposes of addiction.
3. Undergone surgical procedures to correct sleep apnea. A small percentage of patients may be referred to the SDC for post-surgical evaluation of their apnea. This group was likely to be a very small percentage of the sample and were excluded as their apnea has been treated.
4. Not completed the full night diagnostic PSG procedure.
5. PSG diagnosed narcolepsy. Narcolepsy is a REM disorder that has unique sleep characteristics and severe excessive daytime sleepiness.

During initial analysis, subject data were grouped by whether or not the subject had a chronic pain problem. Further grouping of subjects with chronic pain was broken into whether or not they were taking opiate medications. The total number of subjects recruited depended on accruing enough chronic pain patients taking opiates to adequately power the study. Refer to Figure 1 for diagram of group assignment.

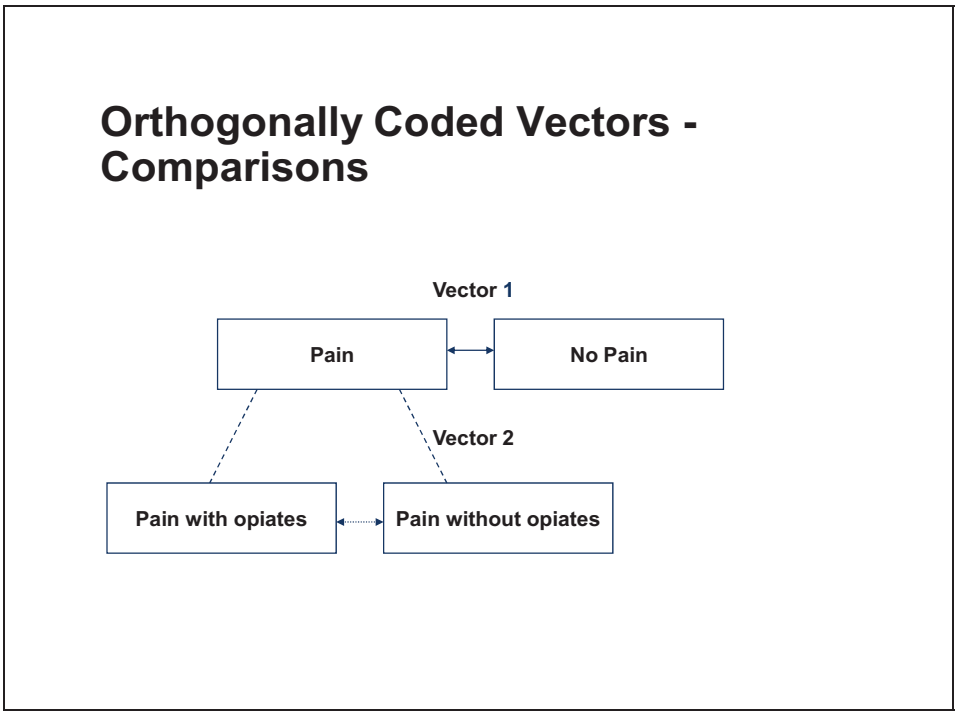

Figure 1. Diagram of group assignment for hypothesis

Power Analysis

To determine the feasibility of the study as well as the sample size necessary to properly power the study, a small pilot study was performed. Following the Health Insurance Portability and Accountability Act (HIPAA) procedures for activities preparatory to research, patients' charts from one month of intake visits at Site A were reviewed. Electronic and paper charts were evaluated to determine the percentage of persons who reported a chronic pain condition and/or use of opiate medications. At site A, 217 patients were seen for initial evaluation during the month of October, 2006. Of those 217 patients, 63 (29%) had a diagnosis which was consistent with a chronic pain problem. Diagnosis consistent with chronic pain was used as a surrogate marker for identifying patients with pain as pain assessment was not documented in the charts. Of the 217 patients, 4 (1.8%) were on long term opiates. Not all records listed all the patient's medications. To assure a large enough sample of patients on opiates, the proportion of subjects with and without chronic pain and taking or not taking opiates found in the pilot study was used in combination with an estimated effect size of 0.75 (standard deviation determined by previous, Wang et al., 2005, study), power = 0.8, and a two-sided alpha = 0.05 to determine the need for at least 20 subjects in the opiate group. In addition, five co-variates were determined and increased the required n of subjects taking opiates to 25. From this pre-study calculation, a projected total of 1356 patients referred to sleep disorders centers were needed to achieve at least 25 subjects experiencing chronic pain and taking opiates. See Figures 2 and 3.

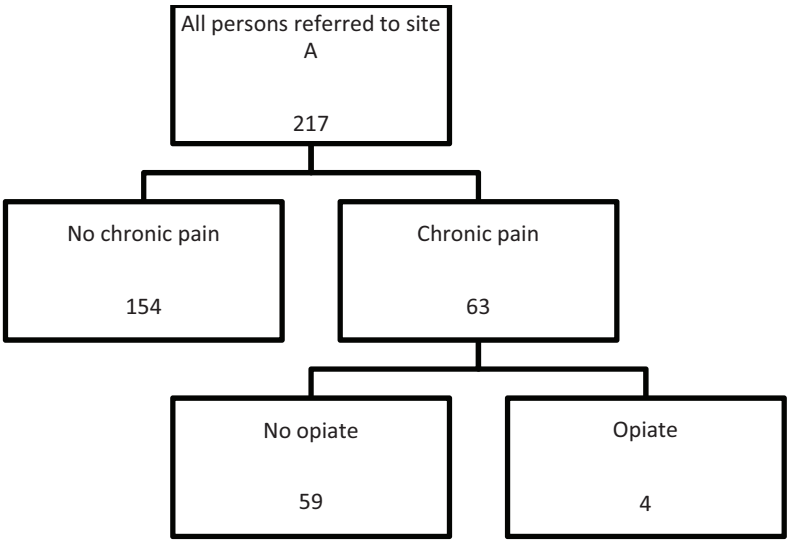

Figure 2. Sample size estimates from feasibility pilot study at site A.

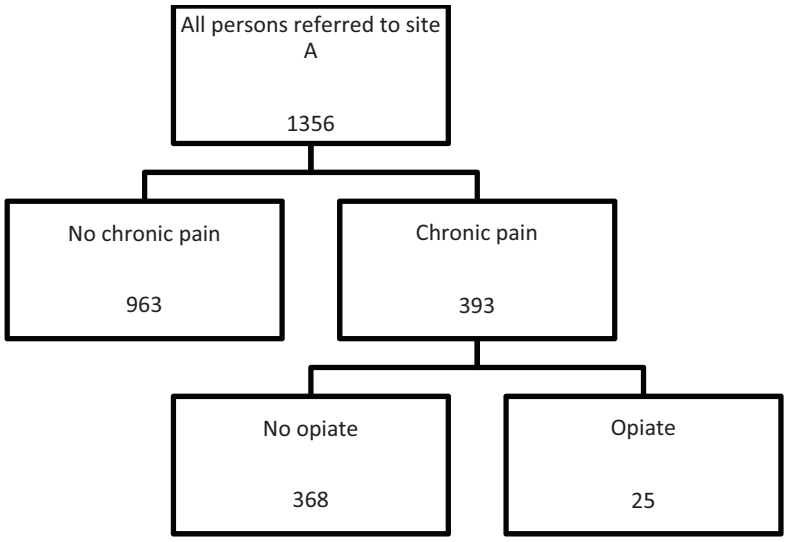

Figure 3. Sample size projected from the feasibility study.

Settings

Three sites, all of which are American Academy of Sleep Medicine accredited were approached to participate in this study. Sites A and B were local facilities that did not routinely collect the information required for this study. Because of this, data at Site A and Site B were collected in prospective studies that required informed consent. Site C routinely collected data necessary for the study, allowing for confidential retrospective collection of data for the same time period as the prospective study was conducted at sites A and B.

Recruitment

Subjects were recruited from sites A and B via letters (see appendices D & E) that they received at their initial intake appointments. An Institutional Review Board approved letter and a copy of the informed consent were handed to potential subjects at their intake appointment. Persons who were interested in participating in the study were asked to read and sign the consent. Investigator contact information was provided on the letter of introduction with instruction to contact the investigator with any questions or desire to clarify study procedures. At site A, the consent was collected by the provider performing the intake examination after giving the subject the opportunity to ask questions. At site B, the consent was collected with the study questionnaire at the time of PSG. The signed consents were then compiled by office staff and held for the investigator in a secured folder. Recruitment was not necessary at site C as the data was retrospectively collected.

Procedures

Data were gathered from the sleep disorders questionnaire, the initial evaluation report written by the examining physician, the medical record, and the report of the PSG procedure. All subjects underwent clinical care as usual and at site A and B additionally completed the Sleep Disorders Questionnaire.

Two sleep center visits occur inside the window of this study for site A & B.

1. Initial sleep center visit included (a) measurement of height, weight, temperature, blood pressure, and pulse; (b) medical history; (c) review of systems; (d) physical examination of EENT, cardiac, pulmonary, and integument systems.
2. Overnight sleep study (polysomnography). On the evening of the sleep study, subjects filled out the Sleep Disorders Questionnaire.

One sleep center visit occurred inside the window of this study for site C. At site C, primary care providers are allowed to prescribe polysomnographic studies according to state law and third party reimbursement guidelines. The sleep medicine doctors do not actually see the patient, they just read the sleep study, their sleep disorders questionnaire and the referral information sent from the PCP to make a diagnosis and prescribe treatment. Because of this, only one sleep center visit occurred inside the window of this study.

Table 8. Operationalization of Study Variables

Measures for Group Assignment in Hypothesis 2			
Construct	*Measurement*	*Variable*	*Source*
Chronic Pain	Categorical 0 = N/1 = Y	Has chronic pain Yes to chronic pain Section I Section III pain intensity reported	Sleep Disorders Questionnaire (SDQ)
Opiate Use	Categorical 0 = N/1 = Y	Uses opiate medications Opiate medication (Section V)	SDQ
Dependent Variables for Sleep Disturbance in Hypothesis 1, 2, and 4			
Sleep Disordered Breathing	Continuous (0-100)	Central Apnea Index(CAI), Obstructive Apnea Index(OAI), Hypopnea Index (HI), Nadir Oxygen Saturation	PSG report
Sleep architecture	Continuous (0-100)	Percent of stages 1, 2, 3/4, & REM sleep	PSG report
Sleep continuity	Continuous (0-300)	Minutes of sleep latency, wake after sleep onset, and number of awakenings	PSG report
Daytime Sleepiness	Continuous (0-24)	Total Epworth Sleepiness Score	SDQ

Table 8. (cont.) *Operationalization of Study Variables*

Measures of Pain and Opiate Use for Hypotheses 1 and 4			
Severity of Pain	Continuous (0-10)	Pain intensity reported at PSG	SDQ
Opiate amount	Continuous (0-2000)	Morphine equivalent daily dose (calculated from opiate dose day of PSG)	SDQ
Risk Factors for all Hypotheses			
Obesity	Continuous (18-50)	Body Mass Index	Clinical record
Age	Continuous (21-100)	Age in years	Clinical record
Gender	Category (0 = M/1 = F)	Gender	Clinical record
Co-morbid diseases	Continuous (0, 1, 2, 3, 4)	Pulmonary, cardiac, neuromuscular, depression disease (# of systems affected by co-morbid diseases)	Clinical record, SDQ
Anatomical abnormalities	Categorical 0 = N/1 = Y	Presence of pharyngeal/oral abnormality or typical morphology/facial profile	Clinical record

Independent Variables

Sleep Disorders Questionnaire

The two page study questionnaire was developed by the investigator for the purpose of gathering information on the independent variables derived from the review of the literature. See Table 8 for operationalizing the variables. If the subject had signed the informed consent (Site A & B), they were asked to fill out the Sleep Disorders Questionnaire (SDQ) while they were awaiting their scheduled bedtime at the lab. Site C routinely administered a sleep disorders questionnaire (see appendix C) resembling the study questionnaire. The SDQ contained questions similar to commonly used health history questionnaires as well as questions derived from specific research instruments. Pertinent reliability and validity information as well as differences from the questionnaire used at site C follows.

Section I – medical problems. Section I of the study questionnaire serves the purpose of gathering a list of the subject's medical problems. Although the list is meant to be inclusive of all their medical problems and tobacco use, medical problems likely to impact sleep outcomes have been explicitly listed. Special attention was given to verify that a pain condition is chronic in nature. For this reason, a definition of >6 months was provided. Subjects' report of medical diagnoses was verified using the referral information from the primary care provider and the initial evaluation note found in the chart. Current or recent (quit < 3 month ago) inhaled tobacco use was considered a co-morbid pulmonary risk factor for analysis. See Table 9. For site C, the medical history portion of the questionnaire specifically inquiring about painful conditions asked if the patient had fibromyalgia, arthritis, or chronic back pain. These questions required a yes or

no answer. No time frame was delineated. If subjects neglected to answer some of the questions, the negative response was assumed. If none of the questions were answered in this section, the data was identified as missing.

Medical diagnoses were converted into categories of systems affected by co-morbid diagnoses. See table 9. For analysis purposes, the number of systems affected by co-morbid diagnoses was used. A similar strategy of using the number of symptoms reported has been used in other studies and found to be effective (Given et al., 2006).

Table 9. Medical Diseases Associated with Sleep Disorders, Categorized by System

Pulmonary	Cardiovascular	Neuromuscular
COPD	Congestive Heart Failure	Multiple sclerosis
Emphysema	Stroke	Myasthenia Gravis
Chronic Bronchitis		Myotonic Dystrophy
Asthma		Lou Gehrig's Disease
Current/recent smoker		
Pulmonary Hypertension		

(Javaheri, 2005; Montplaisir et al., 2005)

.

Section II – Depression. Section II of the study questionnaire screened for active depression. Site C questionnaire contained a depression instrument that included two questions similar to the study questionnaire. (See appendix C). Persons with depression are likely to have sleep architecture changes such as delayed onset of REM sleep and diminished percentage of stage 3 and 4 sleep. Although these screening questions would not exclude the subjects from the study, it may help explain the results that are found. The depression questions chosen for this questionnaire were taken from the Mini International Neuropsychiatric Interview (M.I.N.I.). This interview instrument is widely used in research and clinical practice to screen for acute psychiatric illnesses. The instrument uses two questions to screen for a current depressive episode. When being used as a clinical screening tool, a positive screen would trigger an in-depth interview to confirm the diagnosis of major depressive disease (Sheehan et al., 1998). For the purposes of this study, screening for depressive symptoms was sufficient. Validity testing of MINI patient recorded version as compared to the Structured Clinical Interview for the DSM III-R (SCID) has been reported. The major depressive disorder questions in the patient report version of the MINI were found to be in acceptable agreement (kappa 0.55) with the clinician administered SCID (Sheehan et al., 1998). This instrument has also been used in other community based clinical practices and found to be useful in screening for depression (Cohen, Ofek-Shlomai, Vardy, Weiner, & Shvartzman, 2006). For the purposes of this study, subjects were categorized as depressed if they responded positively to both screening questions. Formal diagnosis of major depressive disease was not needed as the evidence shows that sleep architecture changes occur in the presence of current depressive symptoms. Although the subject may have reported depression in

Section I of the questionnaire, they were not categorized as having active depression unless they answered yes to both depression screening questions. Depression was considered one of the four co-morbid conditions during analysis.

Section III – Pain. Section III of the study questionnaire provided specific subjective measurement of the presence and intensity of pain. These questions were used to confirm the diagnosis of chronic pain as well as to quantify the intensity of the pain.

The most accepted methods for assessing pain intensity in cognitively intact adults are the visual analogue scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS). All the scales are valid and reliable and function equally in the assessment of pain (Gallagher, Bijur, Latimer, & Silver, 2002; Jensen, Karoly, & Braver, 1986). According to Holdgate, Asha, Craig, and Thompson (2003) the VAS and the NRS are highly correlated in measuring acute pain ($r = 0.95$, 95% CI 0.94-0.96). These scales allow the person to report how bad the pain is in relation to the worst pain they can imagine. Please see figure 5 for samples of the three types of pain scales.

According to Dworkin et al. (2005), the difference in pain scales is the ease of use. Dworkin et al. (2005) reviewed pain studies using these three scales and found that studies using the VAS had more missing data. They concluded that this was probably related to the preferred ease of use of the VRS and NRS. The International Association of the Study of Pain consensus report recommends the use of an 11-point NRS for measuring pain intensity in cognitively intact adults (Dworkin et al., 2005).

Although the assessment of chronic pain in clinical practice as well as efficacy trials for pain medications involves a multi-domain assessment, this study only gathered data on the etiology and mechanism (for descriptive purposes), duration (to confirm

chronicity), and intensity (used during analysis of hypothesis 4) of the pain. Assessment of the other domains is not relevant to this research topic.

The questionnaire for site C asked “Do you have any aches or pains? Yes/no. If yes, patients were asked to rate their severity on a scale of 1 (no problem) to 10 (worse imaginable). A negative answer to having pain was coded as a 0, and pain intensity reported 1-10.

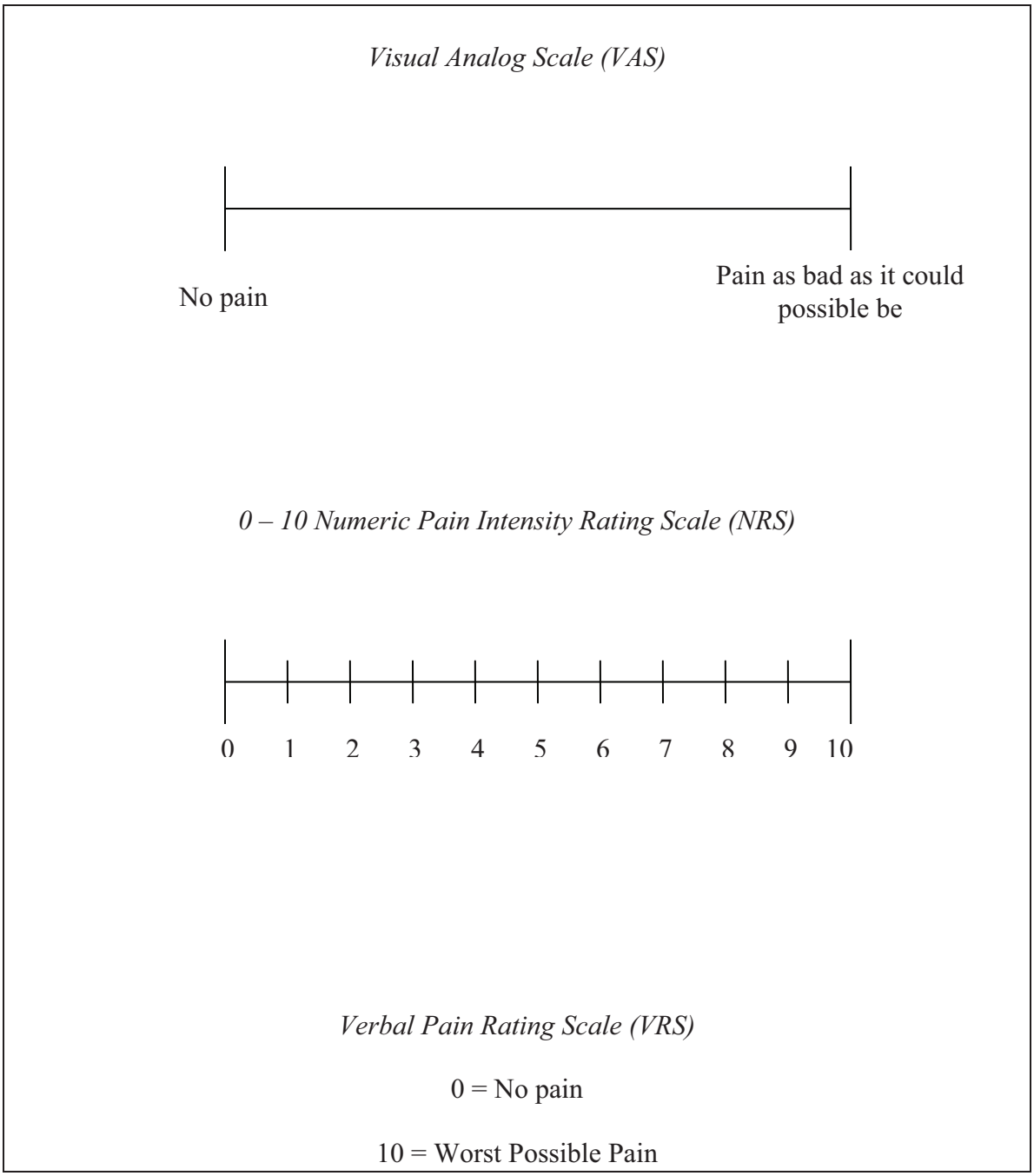

Figure 4. Examples of pain assessment scales.

Section IV - Excessive Daytime Sleepiness. Section IV of the study questionnaire is the Epworth Sleepiness Scale (ESS). This instrument is commonly used in research and clinical practice to quantify excessive daytime sleepiness. The ESS has been found to be highly correlated with obstructive sleep apnea and after treatment for apnea, the ESS scores decreased appropriately (Johns, 1992; Johns, 1994). In addition, the instrument has been found to be internally consistent and test-retest reliable in normal subjects as well as persons with sleep disorders (Johns, 1994). The diagnosis of sleep disordered breathing in part requires the subjective finding of excessive daytime sleepiness (EDS). Daytime somnolence is also a known side effect of opiate medications. The ESS has also been successfully used in studies of agents being tested for effectiveness in treating daytime somnolence in patients taking opiate medications (Slatkin & Rhiner, 2003; Webster, Andrews, & Stoddard, 2003).

The ESS (at all three sites) was scored by the subject on a continuous scale with total score ranging from 0-24. Clinically significant excessive daytime sleepiness is generally considered to be $\geq$10. This instrument is in the public domain.

Section V – Medications. Section V of the study questionnaire provided for the identification of medications that could affect sleep and breathing. The list of medications was meant to be inclusive of all medications the subject was currently taking. This section allowed for the collection of data on opiate use the day of the polysomnography. Opiate dose was used to determine daily morphine equianalgesic dose. Data on all medication use was collected for descriptive purposes only.

Daily morphine equivalent doses of opiates were calculated for hypothesis 1. Equianalgesic doses are anchored on morphine as it is the oldest of the opiates.

Calculations of opiate equivalent doses were based on standards written by the American Pain Society. See Tables 3, 4, and 5. The body of evidence on equianalgesic dose for opiates is based on a few studies as well as empirical data derived from clinical practice. This investigator acknowledges individual differences in metabolism of opiates and that deriving equianalgesic doses is not an exact science due to individual absorption and metabolic differences as well as drug interactions (Mercadante & Bruera, 2006; Mercadante, 2007; Patanwala et al., 2007; Ripamonti, DeConno et al., 1998; Ripamonti, Groff et al., 1998). Given the state of the science in this area, the standard of practice written by the American Pain Society was used.

Dependent Variables

Measurement of Sleep

Sleep was measured using polysomnography (PSG), PSG is the only procedure available for the measurement of sleep architecture and sleep disordered breathing and is considered the gold standard (Academy of Sleep Medicine, 2007; Rechtshaffen & Kales, 1968). In this study, the PSG measures were obtained for clinical purposes during the subject's sleep disorders center overnight diagnostic visit. Technicians at all three sites are certified in standardized polysomnography procedures as well as scoring a polysomnography record according to the Rechtshaffen & Kales and Academy of Sleep Medicine guidelines. Inter-rater reliability of the scoring of polysomnographic records is performed on a regular basis to assure standardization of scoring within the facility. Additionally, all scored records are verified by physicians board certified in sleep medicine by the American Academy of Sleep Medicine.

Polysomnography is used to objectively measure sleep continuity, sleep architecture and respiration during sleep. During the PSG procedure several physiologic sensors are placed on the head, face, chest, and legs to measure: (a) brain electrical activity (EEG), (b) eye and jaw muscle movement (EOG, EMG), (c) leg muscle movement (EMG), (d) airflow for ventilation,(e) respiratory effort, (f) electrocardiogram (EKG), and(g) oxygen saturation. To assure reliability in the technique of acquiring data, all subjects have electrodes placed on the body in identical locations.

During PSG, a person is considered asleep when their EEG transitions from low frequency high amplitude (alpha, beta and gamma) bands to high frequency low amplitude bands (theta and delta). This transition period is called stage 1 sleep and occurs before the other three stages of NREM sleep. During sleep, EEG waveforms transition sequentially through all four stages of sleep. The percentage of sleep stages vary according to age and gender but overall are about 1-5 % stage 1, 55-65% stage 2, 15-20% of stages 3 and 4 combined and about 20-25% REM sleep. During sleep, there is a rotation of cycles of REM and NREM sleep with more REM and stage 2 sleep during the later hours of the night (Walczak & Chokroverty, 1999).

Calculation and definitions of sleep outcome measures

All PSGs were scored in 30-second epochs according to Academy of Sleep Medicine and Rechtschaffen and Kales criteria (Academy of Sleep Medicine, 2007; Rechtshaffen & Kales, 1968). Sleep parameters are reported on the *sleep report.* The sleep report is developed by sleep scoring software and the technicians using the PSG data. The cumulative information on the sleep report is used to diagnose the sleep disorder, as well as provide objective data for analysis of sleep continuity, sleep

architecture, and sleep disordered breathing. As mentioned previously, to ensure validity and reliability of the PSG procedure, physiologic sensors are placed according to the international 10-20 system guidelines using standard placement and equipment for all persons. Three categories of sleep are measured: (a) sleep continuity, (b) sleep architecture, and (c) sleep disordered breathing. Sleep architecture is reported as total minutes and percentage of recording period for stage 1, 2, 3/4, and REM sleep.

The PSG variables for scoring of sleep continuity are defined as (a) sleep latency (SL), the time elapsed from lights off to the first 8 of 10 minutes of any stage of sleep; (b) number of awakenings (NOA), the number of waking intervals >30 seconds and uninterrupted by more than 60 seconds of sleep; (c) wake after sleep onset (WASO), the number of minutes awake from sleep onset to lights on; (d) total sleep time (TST), the sum of all epochs scored as any stage of sleep for the entire recording period and; (e) sleep efficiency (SE), the total sleep time over the duration of the total recording period and reported as a percentage.

Measures for sleep disordered breathing include apnea hypopnea index (AHI), obstructive apnea index (OSI), central apnea index (CSI), mixed apnea index (MAI), hypopneas index (HI), oxygen saturation nadir, and associated arousals from apnea events and oxygen desaturations. The AHI represents the average number of apneic and hypopneic events per hour over the recorded sleep period. An apneic event is defined as the total cessation of airflow for 10 seconds or longer. A hypopneic event is defined as a 30% or greater reduction in airflow that lasts more than 10 seconds along with at least a 3% drop in oxygen saturation or a PSG scored arousal. Apneic events are categorized according to their etiology, central or obstructive. Normal AHI is less than 5 per hour

(Academy of Sleep Medicine, 2007; Guilleminault & Bassiri, 2005). For this study, AHI is not a primary outcome because it represents the combination of two types of apneic events. Hypopnea index was included as a large percentage of patients are known to not present with complete cessation of breath or obstruction of airway.

Central Apnea Index (CAI) represents a loss of inspiratory drive, a component of respiratory depression during sleep due to lack of the central nervous system respiratory centers initiating respiration. A central apneic event is measured during PSG procedure with chest and thoracic belts, airflow sensors placed under the nose, along with standard EEG, EMG, and EOG sensors. A central apneic event is defined as no airflow for at least 10 seconds and no movement on the chest and thoracic belts. More than five per hour is considered clinical meaningful.

Obstructive Apnea Index (OAI) represents a loss of airway flow due to obstruction in the lower pharynx. The index is the average hourly number of obstructive apneic events over the sleep period. An obstructive event is measured during PSG procedure the same as a central event. An apneic event is considered obstructive when there is chest or thoracic movement (effort) but no airflow for 10 or more seconds. More than five events per hour is clinically meaningful.

Mixed Apnea Index (MAI) represents an obstructive apnea in combination with a central apnea event. The usual mixed apnea event represents a lack of respiratory effort directly after the onset of an obstructive event (Parisi, 1999). Because MAI is not a pure measure for either central apnea or obstructive apnea, MAI was not included in the analysis.

Oxygen saturation nadir represents the lowest level of oxygenation during the recorded sleep period. Oxygen saturation is measured as a percentage, and is the percentage of binding sites on the red blood cells in the bloodstream occupied by oxygen. Normally, when red blood cells pass through the lungs they are 95%-100% saturated with oxygen. Oximeter software records continuous oxygen saturations and provides calculations for oxygen saturations over the period of sleep. Oxygenation is reported as mean oxygenation during the night, the number of desaturations below 95% over the sleep period, the total time of oxygenation <95%, and the lowest (nadir) oxygen saturation percentage during the night. For the purposes of primary analysis, the nadir of oxygen saturation was used.

There are 15 sleep variables that could be used in the analysis of each hypothesis. To avoid Type I error, sleep variables entered in the analysis of each hypothesis were chosen to answer specific research questions. The questions were derived from the review of the literature as well as physiologic theory.

Data Collection

Office staff at site A and B placed the signed consents in a folder. The folder was secured for protection of PHI. The investigator then matched the signed consent to the medical record for the purposes of data collection. Using an IRB approved procedure, medical records for all subjects undergoing polysomnographic procedure at site C during the same time frame as site A and B were accessed from the electronic medical record. A data collection instrument was used to compile de-identified data from the medical record. See appendix F data collection instrument. The data collection instrument provided a succinct checklist to guide categorizing the subjects' data into the appropriate

group membership (no chronic pain, chronic non-malignant pain, and chronic non-malignant pain using opiates).

Sites A and B are local clinical sleep disorders centers, which evaluate patients who are complaining of interrupted or non-restorative sleep, excessive daytime sleepiness, or bed partner reports of irregular breathing/snoring during sleep. Site C is a clinical sleep disorders center in the midwestern United States. Patients are referred to site C for the above mentioned reasons. In addition site C receives referrals from a local pain clinic to evaluate most of their patients with pain who are taking opiates. Providers at that pain clinic are concerned about the effects opiates have on sleep disordered breathing so they have chosen to have most of their patients taking opiates for pain evaluated. Collecting data from these three sites was done intentionally to increase the variance in study variables, increase the diversity of the sample, increase the number of pain patients, and decrease the time span of the data collection.

Data Analysis

The Statistical Program for the Social Sciences (SPSS) software for Windows, version 15 was used for data analysis. Prior to entering data into the regression models, measures of central tendency, dispersion and correlations for all demographic, independent and dependent variables were used to assess assumptions of linear regression. Analysis examining differences on ethnicity, gender, and age among the sleep center settings was performed for descriptive purposes. The data were examined for outliers and missing data. Assessment of outliers found one subject's data to be clinically unreasonable so the data was discarded from the dataset.

Missing Data

Missing data on the variable representing the risk factor anatomical abnormalities was substantial at site C (115 out of 128 missing data points). To allow all the subjects' data to be used in the model, the variable mean was imputed to replace all 115 missing data points. The variable mean was also imputed for four other variables with much less frequency of missing data as follows: BMI (3), age (1), Epworth Sleepiness Scale (14), and Pain Intensity (10). Data on the variable opiate dose was also missing for one of the 61 subjects taking opiates. This missing data point was not imputed with the mean and therefore the subject was dropped out of the analysis of hypothesis one and hypothesis three. Per the subject's medical record, he took one morphine pill (no dose recorded) the evening of PSG; but does not take any opiate medication on a daily basis.

See Table 10 for analysis strategy per hypothesis. As there were numerous dependent variables used during the analysis, the possibility of a type 1 error existed. To address this issue, study outcomes were interpreted using clinically logical patterns as opposed to basing findings on single statistically significant findings. See Chapter 5 for interpretation of findings.

Table 10. Analysis Strategy

Hypothesis	Statistical Analysis
H1: Controlling for known risk factors, higher doses of opiates would predict lower percentage of stage 3/4 and REM sleep and higher values of daytime sleepiness, OAI, HI, CAI, and lower oxygen nadir.	Values of OAI, CAI, HI, oxygen nadir, ESS score, percent of stage 3/4 and REM sleep were regressed on dose of opiate medication and known risk factors for sleep disordered breathing.
H2: Controlling for known risk factors, group membership ([no pain vs. pain] and [pain minus opiate treatment vs. pain plus opiate treatment]) would be associated with differences in measures of sleep disordered breathing, sleep architecture, sleep continuity, and/or daytime sleepiness.	Groups were orthogonally coded. The dependent variables (CAI, OAI, HI, oxygen nadir, percentage of sleep stages and continuity, and total Epworth score) were each regressed on the vectors representing group differences and the risk factors.
H3: BMI, age, gender, number of co-morbidities, and presence of anatomical abnormality are independent predictors of the likelihood that a sleep disordered person would report chronic pain.	Simultaneous logistic regression of group membership (pain/no pain) on BMI, age, gender, number of co-morbidities, presence of anatomical abnormality.
H4: Controlling for known risk factors, higher intensity of pain would predict lower CAI, OAI, HI, higher oxygen nadir, lower daytime sleepiness, higher percent of stage 3/4 and REM sleep.	Values of OAI, CAI, HI, oxygen nadir, ESS score, percent of stage 3/4 and REM sleep were regressed on pain intensity and known risk factors for SDB.

Human Subjects Considerations

This study was of minimal risk to subjects. Before starting study procedures, this study was approved by the Institutional Review Board (IRB) for Research Studies at sites A and B. Subjects at sites A and B underwent the informed consent process. The potential subjects were encouraged to read the consent (see appendices G & H) and contact the investigators with questions. Subjects at sites A and B were given a signed copy of their informed consent. A personal health information protection agreement was signed with Site C (see appendix I) to ensure this study would not compromise their patients' privacy under the Health Insurance Portability and Accountability Act (HIPAA). As de-identified data was collected retrospectively from site C, a waiver of informed consent was granted.

Personal health information (PHI) was protected according to HIPAA regulations with HIPAA authorization occurring as part of the informed consent at Sites A and B. At no time was any PHI labeled with identifiers removed from the clinical practice sites.

De-identified data was collected from the clinical records using a data collection instrument. Once data was entered into electronic databases, the information was saved on a secure password protected server. Paper documents were stored in locked cabinets and only accessed by the research team. Study data will be kept for a maximum of seven years.

Chapter 4: Results

This chapter describes the demographic characteristics of the sample as well as the results from the analysis. The results of exploration of each research question will be reported by hypothesis analysis. SPSS statistical software (SPSS for Windows, version 15.0) was used to summarize descriptive data as well as to conduct multiple regression and logistic regression analysis.

Recruitment and Collection of data

Subjects were recruited and data collected between February and June 2008 from three independent sites. A total of 442 subjects were enrolled. Twenty three subjects were excluded per exclusion criteria, leaving 419 subjects finishing the study. The sample consisted of subjects referred to sleep disorder centers site A (n = 205), B (n = 86), and site C (n = 128).

During the data collection phase, it was noted that the local sites performed mostly full night diagnostic polysomnography procedures, and site C performed more split night procedures. These differences were driven by third party reimbursement regulations. The split night procedure consists of observing the patient for 240 minutes of sleep for the purpose of diagnosing their sleep disorder. If at that time they meet the threshold for severe sleep disordered breathing, treatment with CPAP/biPAP is initiated with the titration to appropriate pressure occurring in the second half of the PSG procedure. Some third party payers at site C mandate split night PSG procedures.

The determination of whether the PSG is a full night or is a split night also relies on the severity of sleep disordered breathing. If technicians observe severe reduction in oxygen saturations due to severe sleep disordered breathing, they will initiate the split

night protocol and start treatment even if the patient's study was planned to be full night. During the data collection period at site C, there were six subjects taking opiates that underwent the split night PSG protocol due to the severity of their sleep disordered breathing. These six subjects' data was not included in this analysis because they had not undergone a full night PSG. The other reason for a split night study is titration of CPAP pressure for patients previously on CPAP for sleep apnea. This issue is mentioned to make the reader aware that there were six potential subject's data not included in this analysis because they did not undergo the full night PSG procedure. Those six opiate taking subjects with pain conditions had such severe sleep disordered breathing that their full night PSG was aborted in order to apply treatment. See Table 11 for site specific patient recruitment numbers that describe this issue.

Of the total 419 subjects, 343 met the criteria for sleep disordered breathing (AHI > 5). Three hundred eighteen met the criteria for OSA (AHI > 5 and CAI < 5). Twenty-five subjects met the criteria for CSA (CAI > 5). Of the 25 subjects with CSA, 20 met the criteria for pure CSA (AHI < 5 and CAI > 5). Of those 20 who met the criteria for CSA and not OSA, six were taking opiates and 14 of the 20 reported pain the night of the PSG procedure.

Table 11. Type and Number of Polysomnography Procedures Per Site for Study Period

	Site A	Site B	Site C
Total full night PSG	881	473	129
Split night PSG	20	11	55
Split night/CPAP titration	20	7	16
Split night on opiates	unknown	unknown	6
Enrolled	209	104	129
Excluded due to exclusion criteria	4	18	1
Total finishing study	205	86	128

Sociodemographic Characteristics

The mean age for the entire sample was 49.59 (sd 12.41) with a range of 21-86 years of age. The sample consisted of 49% women and 51% men. Racial breakdown included Caucasian (58%), Black (5%), Hispanic (1%), Biracial (1%), American Indian (<1%), Asian (<1%), other (1%), and unknown/missing (33%). There was considerable missing data on race especially at site C. The mean sample body mass index (BMI) was 33.85 (sd 7.47). See Tables 12 and 13 for comparison of sample characteristics by site and by group.

Fifty nine percent of the sample reported having chronic pain. This percentage was larger than expected and may be due to patients with pain at sites A and B more willing to consent to study participation because the study involved a problem they could relate to. Etiology of subjects' pain was broken down into five categories: disease such as osteoarthritis, rheumatologic conditions, peripheral vascular disease, or neuropathies (67%), accidental injury (10%), cancer (1%), idiopathic (9%), unknown/missing (13%). A total of 61 (14%) subjects reported taking opiate medications on a chronic basis and taking a dose on the day of the PSG. Opiate medications included morphine (18%), oxycodone (49%), methadone (9%), hydrocodone (38%), hydromorphone (1%), and propoxyphene (3%). Thirty-six percent of the subjects taking opiates were taking two different opiate medications. See table 14 for comparison of other medication use between the two groups (pain, no opiate and pain and opiate).

Table 12. Sample Characteristics By Site

	Site A (n = 205)	Site B (n = 86)	Site C (n = 128)
Mean Age	49.6 (11.5)	50.6 (13.1)	48.9 (13.4)
Gender (female)	48.0%	51.0%	48.0%
Mean BMI *	34.3 (7.4)	35.4 (7.1)	32.1 (7.5)
% with pain*	51%	65%	67%
Mean pain intensity	3.0 (2.4)	3.7 (2.4)	4.2 (2.6)
% on opiates*	8%	13%	25%
# cigarettes a day*	2.8 (6.5)	1.0 (3.7)	3.1 (7.0)
# comorbidities	1.1 (0.9)	1.1 (0.9)	0.9 (0.8)
Presence of anatomical abnormality	82%	77%	24%**
Morphine equianalgesic dose*	6.5 (35.1)	10.3 (41.2)	54.6 (151)
Epworth Sleepiness Scale	10.7 (5.4)	9.6 (4.9)	10.1 (5.6)
Apnea Hypopnea Index *	30.2 (26.7)	34.5 (34.1)	16.1 (18.9)
Central Apnea Index*	0.4 (2.2)	1.4 (5.8)	3.2 (9.6)
O2 saturation nadir	82.6 (7.6)	81.7 (8.7)	83.8 (6.6)

*sites significantly different (p. < .05) ** high number of missing data

Table 13. Means of Sleep Variables by Group

	No Pain n=171	Pain/No Opiate n=187	Pain/Opiates n=61
Age	48.0 (12)	50.7 (12)	50.4 (11)
Gender (female)**	37%	55%	64%
BMI**	32.9 (6)	34.9 (8)	32.8 (7)
# comorbidities**	.77 (.7)	1.18 (.9)	1.48 (.9)
Presence of AA	81%	82%	83%
CAI	1.6 (7)	1.1 (4)**	5.0 (13)**
OAI	6.7 (14)	9.4 (14)	4.4 (9)
HI	15.3 (18)	15.6 (15)	11.6 (13)
MAI	1.3 (4)	2.4 (8)	1.5 (6)
AHI	25 (27)	28.7 (26)	22.7 (25)
Oxygen sat nadir %	82.9 (7)	82.5 (7)	83.5 (6)
ESS	10.7 (5)	9.7 (5)	10.8 (5)
Stage 1 %	8.7 (7)**	10.2 (8)**	7.3 (8)**
Stage 2 %	67.4 (13)	64.9 (12)**	71.3 (15)**
Stage 3/4 %	6.4 (10)	7.1 (9)	8.5 (11)
REM %	16.8 (10)	19.1 (10)	14.0 (14)
SL min.	31.2 (32)	28.0 (32)	30.8 (36)
TST min.	338.5 (69)	347.5 (72)	336.8 (67)
NOA	18.2 (12)	17.1 (14)	19.0 (13)
SE %	77.6 (14)	81.0 (13)	78.1 (13)

**statistically significant p. <.05

Table 14. Other Medication Use

Medication	No Pain (n = 171)	Pain/No opiate (n = 187)	Pain/Opiate (n = 61)
Antidepressant	25.1%	30%	18%
Anticonvulsant	4.7%	13%	10%
Benzodiazepine	6.4%	7%	6%
Muscle Relaxant	1.2%	4%	7%
Tramadol	0	3%	<1%
Antihypertensive	26.3%	42.2%	36.1%

As differences among the three sites were clinically reasonable and added appropriate diversity to the sample, and variables were measured using like procedures, site was not entered into the analysis models. Prior to performing regression analysis, correlation analysis was performed to assess for collinearity and clinically reasonable relationships. Per the correlation matrix, predicting variables all had a correlation coefficient of less than 0.4 with the dependent variables. Statistically significant correlations between variables were in the theoretically appropriate direction. Additional check of collinearity was performed by inspecting tolerance levels in the regressions. All tolerances ranged between .8 and .9.

As a whole, the sample is representative of patients who have sleep disturbance related to sleep disordered breathing. Subjects were on average obese, middle aged, excessively sleepy during the day, and had a higher prevalence of hypertension, diabetes mellitus and depression than the population at large. Eighty-two percent of the subjects had an AHI > 5 (clinically relevant SDB). Six percent of the subjects had a CAI > 5.

An alpha level of .05 was used for all statistical tests.

Results per Hypothesis

Hypothesis One

To determine the relationship between opiate dose and measures of sleep and sleep disordered breathing, values of each dependent variable (CAI, OAI, HI, oxygen nadir, percent of stage 3/4 sleep, and score of the Epworth Sleepiness Scale) were individually hierarchically regressed on opiate dose (mg.) controlling for known risk factors (age, BMI, gender, number of co-morbidities and presence of anatomical

abnormalities). Risk factors were entered in step one and opiate dose entered as step two of the model.

Hypothesis one was only partially supported by the results of this study. Opiate dose predicted higher CAI and higher percent of stage 3/4 sleep. Opiate dose did not predict OAI, HI, oxygen saturation nadir, or excessive daytime sleepiness.

Central Apnea Index. Step one of the model (risk factors) was statistically significant (F (5, 412) = 2.597, p. = .025) and predicted 3.1% (R square change) of the variance in the central apnea index. Of the risk factors, only age (b = .063, p. = .011) significantly predicted central sleep apnea. Higher age predicted a higher CAI. Step two of the model (opiate dose in mg.) was a statistically significant increment (F (1,411) = 85.317, p. = <.001) and predicted an additional 16.7% (R square change) of the variance in the central apnea index. Controlling for risk factors, the unstandardized regression coefficient (b) for opiate dose was 0.028, p = <.001. Controlling for opiate dose, age (b = .08, p. = <.001) and gender (b = -1.225, p. = .030) were also predictors of CAI. Being male and older age predicted a higher CAI. The model predicts that, all other risk factors being equal, a patient on 100 mg. of opiate could be expected to display a central apnea index that is 2.8 episodes/ hr. higher than a patient not taking opiate medications.

Obstructive Apnea Index. Step one of the model (risk factors) was statistically significant (F (5, 412) = 7.835, p. = <.001) predicting 8.7% of the variance in the OAI. Unique predictors for OAI were age (b = .126, p. = .025), male gender (b = -7.014, p. = <.001) and, BMI (b = .276, p. = .005). Male gender was the strongest predictor of OAI. Older age and higher BMI also predicted higher OAI. Step two of the model did not

predict a significant amount of additional variance in OAI (F (1,411) = .825, p. = .364). Controlling for risk factors, opiate dose did not predict obstructive apnea index.

*Hypopnea Inde*x. Step one of the model (risk factors) was statistically significant (F (5, 412) = 22.600, p. = < .001) predicting 21.5% of the variance in the HI. Unique predictors for HI were male gender (b = -4.132, p. = .007), higher BMI (b = .996, p. = < .001), and presence of anatomical abnormalities approached significance (b = 4.653, p. = .053). Step two of the model, addition of opiate dose, did not predict a significant amount of additional variance in HI (F (1,411) = .412, p. = .522).

Oxygen Saturation Nadir. Step one of the model (risk factors) was statistically significant (F (5, 412) = 19.979, p. = < .001) predicting 19.5% of the variance in the oxygen saturation nadir. Unique predictors for higher (more desirable) oxygen saturation nadir were younger age (b = -.115, p. = < .001), female gender (b = 2.983, p. = < .001), lower BMI (b = -.339, p. = < .001), lack of anatomical abnormalities (b = -2.947, p. = .006). Step two of the model, adding opiate dose, did not predict a significant additional amount of the variance in oxygen saturation nadir (F (1, 411) = .057, p. = .811).

Percentage of Stage 3/4 Sleep. Step one of the model (risk factors) was statistically significant (F (5, 412) = 9.011, p = < .001) predicting 9.9% of the variance in stage 3/4 sleep. Unique predictors for increased percent of stage 3/4 sleep were young age (b = -.143, p. = < .001), female gender (b = 4.450, p. = < .001), and lower BMI (b = -.216, p. = .001). Step two of the model was a statistically significant increment (F (1,411) = 4.754, p. = .030) and predicted an additional 1% (R square change) of the variance in the percent of stage 3/4 sleep. Controlling for opiate dose, four of the risk factors significantly predicted higher percent of stage 3/4 sleep (see table 15). Female

gender is the strongest predictor of a higher percent of stage 3/4 sleep. Opiate dose was also a significant predictor of percent of stage 3/4 sleep (b = .011, p. = .030). The model predicts that, all other risk factors being equal, a patient on 100 mg. of opiate could be expected to have 1.1 percent more stage 3 and 4 sleep than a patient not taking opiate medications.

Table 15. Regression Coefficients for Dependent Variable Percent of Stage 3/4 Sleep

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig
Age	-.136	.037	-.172	-3.652	< .001
Gender	4.407	.933	.225	4.722	< .001
BMI	-.194	.066	-.148	-2.958	.003
Co morbidities	-1.041	.520	-.096	-2.002	.046
Anatomical Abnormalities	2.325	1.460	.076	1.593	.112
Morphine Equianalgesic Dose	.011	.005	.104	2.180	.030

Percent of REM sleep. Step one of the model (risk factors) was statistically significant (F (5, 412) = 3.193, p. = .008) predicting 3.7% of the variance in the percent of REM sleep. Unique predictors for higher percent of REM sleep were, lower BMI (b = -.149, p. = .041) and lower number of comorbidities (b = -1.155, p. = .047). Step two of the model, adding opiate dose, did not predict a significant additional amount of the variance in percent of REM sleep (F (1, 411) = .908, p. = .341).

Total score on Epworth Sleepiness Scale. Step one of the model (risk factors) was not statistically significant (F (5, 412) = 2.158, p. = .061). The risk factors used in this model were not significant predictors of the total score on the Epworth Sleepiness Scale. Step two of the model also was not statistically significant (F (1,411) = .417, p. = .519). Controlling for risk factors for sleep disordered breathing, opiate dose was not a predictor of total Epworth Sleepiness Scale.

Post Hoc analysis on mixed apnea index. Step one of the model (risk factors) was statistically significant (F (5,412) = 4.644 = p< .001) accounting for 5.3% of the variance in MAI. Male gender was a significant predictor (b = -3.073, p. = < .001) of mixed apnea events. Step two of the model (opiate dose) did not predict a statistically significant increment in variance (F (1, 411) = .062, p. = .804).

Hypothesis Two

To determine the relationship between pain and measures of sleep disordered breathing, sleep architecture and sleep continuity, values of each dependent variable (CAI, OAI, HI, oxygen nadir, percent of SWS, and score of the Epworth Sleepiness Scale, percent of stage 1, 2, 3/4, and REM sleep, SL, TST, number of awakenings & SE) were individually hierarchically regressed on orthogonally coded vectors representing

groups of subjects ([no pain vs. pain] and [pain minus opiate treatment vs. pain plus opiate treatment]), controlling for known risk factors (age, BMI, gender, number of co-morbidities and presence of anatomical abnormalities). Risk factors were entered in step one and vectors representing groups entered simultaneously as step two of the model. See table 16 for coding of vectors.

Hypothesis two was partially supported by the results of this study. Group membership (pain plus opiate treatment) predicted CAI, percent of stage 1, 2 and REM sleep. Measures of sleep continuity, OAI, HI, oxygen nadir, excessive daytime sleepiness, and percent of stage 3/4 were not predicted by group.

Table 16. Coding for Vectors

Group	Vector 1	Vector 2
No pain (n = 171)	248	0
Pain minus opiate treatment (n = 187)	-171	-61
Pain plus opiate treatment (n = 61)	-171	187

Note. Vector correlation confirmed, r = 0.

Central Apnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5, 413) = 2.569, p. = .026) predictors of increased CAI values, with increased age the unique predictor and predicting 3% (R square change) of the variance. Step two of the model (group) was a statistically significant increment (F (2,411) = 13.618, p = < .001) and predicted an additional 6% (R square change) of the variance in the central apnea index. The unstandardized regression coefficient (b) for the vector comparing pain versus no pain was not statistically significant (b = -.002, p. = .268). The unstandardized regression coefficient (b) for the vector comparing pain and

opiates vs pain without opiates was significant (b = .019, p. = < .001). There was no mean difference in CAI between subjects with and without pain. Mean central sleep apnea index was significantly higher in patients with chronic pain plus opiate treatment (M 5.0, sd 13) as compared to subjects with chronic pain minus opiates (M 1.1, sd 4).

Obstructive Apnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant predictors (F (5,413) = 7.869, p. = < .001) of OAI values, with older age, male gender, and higher BMI unique predictors and predicting 8.7% (R Square change) of the variance. Step two of the model did not predict a significant increment in variance in OAI (F (2,411) = 1.932, p. = .146). The mean obstructive apnea index was not significantly different between subjects with and without pain, or between subjects with pain that were and were not on opiates.

Hypopnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5, 413) = 22.667, p. = < .001) predictors of OAI values, with male gender and higher BMI unique predictors of 21.5% (R square change) of the variance in HI. Step two of the model (group) did not predict a significant increment in the amount of variance in HI (F (2, 411) = 1.478, p. = .229). Hypopnea index was not significantly different between subjects with and without pain, or between subjects with pain that were and were not on opiates.

Oxygen saturation nadir. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5, 413) = 20.028, p. = < .001) predictors of oxygen saturation nadir, with younger age, female gender, lower BMI, and absence of anatomical abnormalities unique predictors of 19.5% (R square change) of the variance in oxygen saturation nadir. Step two of the model (group) did not predict a significant

increment in the amount of variance in oxygen saturation nadir (F (2, 411) = .859, p. = .424). Mean oxygen saturation nadir was not different between subjects with and without pain, or between subjects with pain that were and were not on opiates.

Total score on the Epworth Sleepiness Scale. As demonstrated in the analysis for hypothesis 1, risk factors were not significant (F (5, 413) = 2.183, p. = .055) predictors of total score on the Epworth Sleepiness Scale. Step two of the model (group) also was not a statistically significant increment (F (2, 411) = .1.077, p. = .342). Controlling for risk factors, the total score on the Epworth Sleepiness Scale was not significantly different between subjects with and without pain, or between subjects with pain that were and were not on opiates.

Percent of Stage One Sleep. Step one of the model (risk factors) was statistically significant (F (5, 413) = 6.078, p. = < .001) and predicted 6.9% (R squared change) of the variance in the percentage of stage 1 sleep. Of the risk factors, older age (b = .111, p. = .001), male gender (b = -2.814, p. = .001), and higher BMI (b = .167, p. = .003) significantly predicted higher percent of stage one sleep. Step two of the model (group) was a statistically significant increment (F (2, 411) = 3.284, p. = .038) and predicted an additional 1.5% (R-square change) of the variance in percent of stage on sleep. The unstandardized regression coefficient (b) for the vector comparing pain versus no pain was statistically significant (b = .005, p. = .024). The unstandardized regression coefficient (b) for vector comparing pain and opiates versus pain without opiates was not significant (b = -.006, p. = .209). Mean percent of stage 1 sleep was significantly higher in subjects without pain (M 8.7, sd 7) as compared to subjects with pain (M 7.3, sd 8).

Percent of Stage 2 Sleep. Step one of the model (risk factors) was statistically significant (F (5, 413) = 2.257, p. = .048) and predicted 2.7% (R square change) of the variance in percent of stage 2 sleep. Of the risk factors, higher BMI (b = .190, p. = .031) and number of co morbidities (b = 1.417, p. = .043) significantly predicted higher percent of stage 2 sleep. Step two of the model (group) was a statistically significant increment (F (2, 411) = 5.402, p. = .005) and predicted an additional 2.5% (R square change) of the variance in percent of stage two sleep. The unstandardized regression coefficient (b) for group (pain versus no pain) was not statistically significant (b = -.005, p. = .128). The unstandardized regression coefficient (b) for group (pain and opiates vs pain without opiates) was significant (b = .022, p. = .003). Mean percent of stage two sleep is significantly higher in chronic pain patients taking opiates (M 71.3, sd 15) than chronic pain patients not taking opiates (M 64.9, sd 12).

Percent of Stage 3 And 4 Sleep. Step one of the model (risk factors) was statistically significant (F (5, 413) = 9.102, p. = < .001) and predicted 9.9% (R square change) of the variance in percent of stage 3/4 sleep. Of the risk factors, younger age (b = -.144, p. = < .001), female gender (b = 4.466, p. = < .001), and lower BMI (b = -.216, p. = .001) significantly predicted higher percent of stage 3/4 sleep. Step two of the model (group) was not statistically significant (F (2, 411) = .884, p. = .414). Mean percent of stage 3/4 sleep did not differ between subjects with and without pain; or of subjects with pain, whether or not they were taking opiates.

Percent of REM Sleep. Step one of the model (risk factors) was statistically significant (F (5, 413) = 3.147, p. = .008) and predicted 3.7% (R square change) of the variance in the percentage of REM sleep. Of the risk factors, lower BMI (b = -.149, p. =

.042) significantly predicted higher percent of REM sleep. Step two of the model (group) was also statistically significant (F (2, 411) = 3.598, p. = .028) and predicted an additional 1.7% (R-square change) of the variance in percent of REM sleep. The unstandardized regression coefficient (b) for the vector representing group (pain versus no pain) was not statistically significant (b = .003, p. = .221). The unstandardized regression coefficient (b) for vector representing group (pain and opiates vs pain without opiates) was significant (b = -.015, p. = .016). Mean percent of REM sleep was significantly higher in subjects with pain not taking opiates (M 19.1, sd 10) as compared to subjects with pain taking opiates (M 14.0, sd 14).

Latency to Sleep Onset. Step one of the model (risk factors) was not statistically significant (F (5, 401) = 1.919, p. = .090). Risk factors were not predictors of sleep latency. Step two of the model (group) did not predict a significant increment in the amount of variance in sleep latency (F (2, 399) = .226, p. = .798). Controlling for risk factors mean sleep latency was not different between subjects with and without pain, or between subjects with pain that were and were not taking opiates.

Total Sleep Time. Step one of the model (risk factors) was statistically significant (F (5, 413) = 6.330, p. = < .001) and predicted 7.1% (R square change) of the variance in total sleep time. Of the risk factors, younger age (b = -.833, p. = .002), female gender (b = 22.711, p. = .001), and lower BMI (b = -1.260, p. = .009) significantly predicted greater total sleep time. Step two of the model (group) was not statistically significant (F (2,411) = .767, p. = .465). Controlling for risk factors, mean total sleep time did not differ between subjects with and without pain; or of subjects with pain, whether or not they were taking opiates.

Number of Awakenings. Step one of the model (risk factors) was not statistically significant (F (5, 413) = 1.188, p. = .314). None of the risk factors were predictive of number of awakenings. Step two of the model (group) was also not a statistically significant increment (F (2, 411) = .633, p. = .532). Total number of awakenings during sleep period did not differ between subjects with and without pain; or of subjects with pain, whether or not they were taking opiates.

Sleep Efficiency. Step one of the model (risk factors) was statistically significant (F (5, 413) = 3.926, p. = .002) and predicted 4.5% (R square change) of the variance in sleep efficiency. Of the risk factors, younger age (b = -.164, p. = .003), and female gender (b = 2.710, p. = .050) significantly predicted greater sleep efficiency. Step two of the model (group) was not a statistically significant increment (F (2, 411) = 2.126, p. = .121). Controlling for risk factors, mean sleep efficiency did not differ between subjects with and without pain; or of subjects with pain, whether or not they were taking opiates.

Post Hoc Analysis on Mixed Apnea Index. Step one of the model (risk factors) was statistically significant (F (5, 413) = 4.621, p. = < .001 contributing 5.3% (R square change) of the variance in the mixed apnea index. Male gender was a significant predictor (b = -3.073, p. = < .001) of mixed apnea events. Step two of the model was not a statistically significant predictor (F (2, 411) = .332, p. = .718) of incremental variance in MAI.

Hypothesis Three

To assess if the risk factors for sleep disturbance differ in subjects experiencing chronic pain compared to subjects without pain, the likelihood of having chronic pain

was simultaneously logistically regressed on variables representing known risk factors (age, BMI, gender, number of co-morbidities and presence of anatomical abnormalities).

Hypothesis three was partially supported by this study. Gender, age and number of co morbidities were independent predictors that a person would report chronic pain. The number of anatomical abnormalities and BMI were not predictors of chronic pain.

The logistic regression model assessing the likelihood of the five risk factors predicting chronic pain was statistically significant (-2 log likelihood = 518.705, Chi-square (5 df) = 47.921, p. = < .001). Controlling for other risk factors, older age, female gender, and higher number of co morbid conditions were statistically significant predictors that a subject would report pain. Controlling for the other risk factors in the model, for every increase of 1 in the number of comorbidities, the likelihood of reporting chronic pain increases by a factor of 1.841 (OR 1.841, 95% CI 1.427 to 2.379); and for every 1 year increase in age, the likelihood of reporting chronic pain increases by a factor of 1.017 (OR 1.017, 95% CI 1.000 to 1.034). Females are nearly twice as likely to report chronic pain as compared to males (OR .485, 95% CI .318 to .738). Descriptive analysis by group was performed to verify results of hypothesis three. See table 17.

Table 17. Descriptive Statistics for Risk Factors by Group

	No Pain	Pain
Age	M 48.0 (sd 12.6)	M 50.6 (sd 12.1)
Gender	37% female	57% female
BMI	M 33.0 (sd 6.8)	M 34.5 (sd 7.8)
Anatomical Abnormality Present	81%	83%
# Comorbidities	.77 (sd .8)	1.25 (sd .9)

Hypothesis Four

To determine the relationship between pain intensity at time of polysomnography and sleep measures, values of each dependent variable (CAI, OAI, HI, oxygen nadir, score of the Epworth Sleepiness Scale, percent of stage 3/4 and REM sleep) were individually hierarchically regressed on pain intensity (0-10 scale) controlling for known risk factors (age, BMI, gender, number of comorbidities and presence of anatomical abnormalities). Risk factors were entered in step one and pain intensity was entered as step two of the model.

Hypothesis four was also partially supported by this study. Pain intensity was a significant predictor of CAI, OAI, and percent of REM sleep. Pain intensity was not a significant predictor of HI, oxygen saturation, stage 3/4 sleep or excessive daytime sleepiness.

After examination of findings, it became apparent that findings may be spurious as some patients with pain were also taking opiates. To examine this possibility, the dependent variables were re-run controlling for opiate dose. Both model results on variables with significant findings are reported.

Central Apnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant ($F(5, 413) = 2.569$, $p. = .026$) predictors of CAI values, with increased age and male gender unique predictors. Step two of the model (pain intensity) was a statistically significant increment ($F(1, 412) = 23.961$, $p. = < .001$) and predicted an additional 5.3% (R-square change) of the variance in the central apnea index. The unstandardized regression coefficient (b) for pain intensity was 0.554, $p = < .001$. The model predicts that, all other risk factors being equal, for every 1 point increase

in pain intensity the patient could be expected to display a central apnea index that is 0.554 episodes/ hr. higher than a patient without any pain.

Opiate dose was added as step two of the model to assess for spurious findings related to opiates. Step one of the model remained statistically significant (F (5, 412) = 2.597, p. = .025. Step two of the model (opiate dose) was a statistically significant increment (F (1,411) = 85.317, p. = < .001 and predicted an additional 16.7% (R square change) of variance in central apnea index. The unstandardized regression coefficient (b) for opiate dose was .028, p. = < .001. Step three of the model (pain intensity) remained a statistically significant increment (F (1, 410) = 6.841, p. = .009) and predicted an additional 1.3% (R-square change) of the variance in central apnea index. The unstandardized regression coefficient (b) for pain intensity was .288, p. = .009. Controlling for risk factors and opiate dose, pain intensity is a significant predictor of central apnea index. For every 1 point increase in pain intensity the patient could be expected to display a central apnea index that is 0.288 episodes/ hr. higher than a patient without any pain.

Obstructive Apnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5, 413) = 7.869, p. = < .001) predictors of OAI, with older age, male gender, and higher BMI unique predictors of higher OAI values. Step two of the model (pain intensity) was a statistically significant increment (F (1, 412) = 5.478, p. = .020) and predicted an additional 1.2 % (R-square change) of the variance in the obstructive apnea index. The unstandardized regression coefficient (b) for pain intensity was -0.618, p = .020. The model predicts that, all other risk factors being

equal, for every 1 point increase in pain intensity the patient could be expected to display an obstructive apnea index that is 0.618 episodes/hr. lower than a patient without pain.

Opiate dose was added as step two of the model to control for possible spurious findings related to opiates. Step one of the model remained statistically significant (F (5, 412) = 7.835, p. = < .001. Step two of the model (opiate dose) was not a statistically significant increment (F (1,411) = .825, p. = .364) in obstructive apnea index. Step three of the model (pain intensity) remained a statistically significant increment (F (1, 410) = 4.671, p. = .031) and predicted an additional 1% (R-square change) of the variance in obstructive apnea index. The unstandardized regression coefficient (b) for pain intensity was -.599, p. = .031. Controlling for risk factors and opiate dose, pain intensity is a significant predictor of obstructive apnea index. For every 1 point increase in pain intensity the patient could be expected to display an obstructive apnea index that is 0.599 episodes/ hr. lower than a patient without any pain.

Hypopnea Index. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5, 413) = 22.667, p. = < .001) predictors of HI values, with male gender and higher BMI unique predictors of higher values. Step two of the model did not predict a significant increment of variance in HI (F (1, 412) = 3.057, p. = .081). Controlling for the risk factors, pain intensity was not significant predictor of the Hypopnea index.

Oxygen Saturation Nadir. As demonstrated in the analyses for H1, the risk factors as a group were statistically significant (F (5,413) = 20.028, p. = < .001). Younger age, female gender, lower BMI, and absence of anatomical abnormalities were all unique predictors of higher oxygen saturation nadir. Step two of the model (pain intensity) did

not predict a significant increment in the variance of oxygen saturation nadir (F (1, 412) = .012, p. = .914). Controlling for the risk factors, pain intensity was not a significant predictor of oxygen saturation nadir.

Total Score on the Epworth Sleepiness Scale. As demonstrated in the analysis for hypothesis 1, risk factors were not significant (F (5, 413) = 2.183, p. = .055) predictors of total score on excessive daytime sleepiness. Step two of the model also was not statistically significant (F (1, 412) = 1.278, p. = .259). Controlling for risk factors, pain intensity was not a predictor of the total score on the Epworth Sleepiness Scale.

Percent of Stage 3/4 Sleep. As demonstrated in the analyses for H2, the risk factors as a group were statistically significant (F (5,413) = 9.102, p. = < .001) predictors of stage 3/4 sleep, with younger age, lower BMI and being female predictors of higher percent of stage 3/4 sleep. Step two of the model (pain intensity) was a statistically significant increment (F (1, 412) = 4.885, p. = .028) and predicted an additional 1.1 % (R-square change) of the variance in the percent of stage 3/4 sleep. The unstandardized regression coefficient (b) for pain intensity was .389, p = .028. The model predicts that, all other risk factors being equal, for every 1 point increase in pain intensity the patient could be expected to display .389 percent more stage 3/4 sleep than a patient without pain.

Opiate dose was added as step two of the model to control for possible spurious findings related to opiates. Step one of the model remained statistically significant (F (5, 412) = 9.011, p. = < .001. Step two of the model (opiate dose) was a statistically significant increment (F (1, 411) = 4.754 p. = .030) in percent of stage 3/4 sleep. The unstandardized regression coefficient (b) was .011, p. = .030. Step three of the model

(pain intensity) was not a statistically significant increment (F (1, 410) = 2.692, p. = .102). Controlling for risk factors and opiate dose, pain intensity is not a significant predictor of percent of stage 3/4 sleep.

Percent of REM Sleep. As demonstrated in the analyses for H2, the risk factors as a group were statistically significant (F (5,413) = 3.147, p. = .008) predictors of REM sleep, with more comorbidities and higher BMI were predictors of REM lower percent of REM sleep. Step two of the model (pain intensity) was a statistically significant increment (F (1, 412) = 6.217, p. = .013) and predicted an additional 1.4 % (R-square change) of the variance in the percent of REM sleep. The unstandardized regression coefficient (b) for pain intensity was -0.491, p = .013. The model predicts that, all other risk factors being equal, for every 1 point increase in pain intensity the patient could be expected to display REM sleep 0.491 percent lower than a patient without pain.

Opiate dose was added as step two of the model to control for possible spurious findings related to opiates. Step one of the model remained statistically significant (F (5, 412) = 3.193, p. = .008. Step two of the model (opiate dose) did not predict a statistically significant increment (F (1, 411) = .908 p. = .341) in percent of REM sleep. Step three of the model (pain intensity) remained a statistically significant increment (F (1, 410) = 5.288, p. = .022) and predicted an additional 1.2 % (R-square change) of the percent of REM sleep. The unstandardized regression coefficient (b) for pain intensity was -.465, p. = .022. Controlling for risk factors and opiate dose, pain intensity is a significant predictor of percent of REM sleep. For every 1 point increase in pain intensity the patient could be expected to display .475 percent less REM sleep than a patient without any pain.

Risk Factors

Using the previously published evidence, known risk factors for sleep disturbance, sleep disordered breathing, and pain were added to the regression equations to enhance the prediction models. Five known risk factors for sleep disturbance and sleep disordered breathing were included. Not all five factors turned out to account for significant variance in the dependent variables. In particular, number of comorbidities and presence of anatomical abnormalities were not consistent predictors. See table 18.

Table 18. Significant Predictors for Higher Level on Dependent Variables

Dependent Variable	Age	Gender	BMI	Anatomical Abnormalities	Number of Comorbidities
Central Apnea Index	older				
Obstructive Apnea Index	older	male	higher		
Hypopnea Index		male	higher	presence of	
Mixed Apnea Index		male			
Apnea Hypopnea Index	older	male	higher	presence of	
Oxygen Saturation Nadir	younger	female	lower	lack of	
Epworth Sleepiness					
Scale					
Total Sleep Time	younger	female	lower		
Sleep Latency					
Number of Awakenings					
Sleep Efficiency	younger	female			
Stage 1	older	male	higher		
Stage 2			higher		higher
Stage 3/4	younger	female	lower		lower
REM			lower		lower
Presence of Pain	older	female			higher

Chapter 5: Discussion

The findings from this study will contribute to the knowledge base of providers who prescribe opiate medications for the treatment of chronic pain. Using a physiologically based theory, this study provided knowledge about the effects opiates have on sleep and breathing during sleep in patients with chronic pain. While interpreting the results it is important to remember that 82% of the subjects in this study had clinically relevant (AHI > 5) sleep disordered breathing; and all subjects had complaints of sleep disruption or were thought to be at risk of sleep disruption or sleep disordered breathing by their referring provider.

The Relationship between Chronic Pain, Opiates and Sleep Disordered Breathing

Opiates (even when used long term and at chronic doses) are associated with central sleep apnea. Patients with chronic pain taking opiates can expect to have as many as 5 $\pm$ 13 central apneic events per hour as compared to 1.6 $\pm$ 7 events per hour in patients without pain and not taking opiates. The relationship between opiates and central sleep apnea is dose dependent as Webster, et. al, 2008 has previously reported. This study data predicted that a patient on 100 morphine equivalent milligrams of opiate medication could be expected to display a central apnea index 2.8 events per hour higher than a patient not taking opiates. If taking 200 mg. of morphine, or an equivalent of a different opiate, a patient may be at risk of meeting the diagnostic criteria (CAI $\geq$ 5) for central sleep apnea. In this study there were 18 subjects taking more than 200 mg. of morphine equivalent opiate the day of the PSG procedure. Eight of the eighteen presented with a CAI > 5; only two of the eight met the criteria for OSA. In looking for trends in characteristics of the six subjects with pure CSA, the subjects differed on which opiate

medication they were taking. There were no consistent presences of benzodiazepines, antidepressants, smoking, or other medical conditions that are known to be associated with CSA.

Theoretically, this finding seems reasonable as opiates are thought to exert their major effect by depressing the central nervous system. What is not clear at this point in development of this field of research is if this finding holds any clinical relevance. Applying the recent research from the potential negative health impact of OSA, it is reasonable to theorize that intermittent hypoxia may mediate the development of hypertension and alter glucose metabolism in patients with CSA. According to previous work by Teichtahl et al. (2005) patients taking methadone at chronic and stable doses have blunted central chemoreceptor responses to hypoxia and hypercapnia. If this finding was present in the subjects in this study, it seems plausible that the opiate group would present with lower oxygen saturation nadirs. But in fact, the subjects in the opiate group did not have significantly lower oxygen saturation nadirs than the other two groups. They exhibited clinically relevant hypoxia (mean oxygen saturations nadir 82%) equal to the subjects not taking opiates. Not known from this study is whether patients taking opiates spend as much or more time at lower oxygen saturations than patient's not taking opiates; remembering that most subjects in this comparison group had OSA.

Other measures of sleep disordered breathing (obstructive apnea index, hypopnea index, oxygen saturation nadir or excessive daytime sleepiness) did not have a dose dependent relationship with opiates. Nor did patients taking opiates differ on these other measures of SDB as compared to subjects with pain plus opiate or without pain. Interestingly, patients with pain had on average significantly lower obstructive apnea

index than patients without pain. This provides some preliminary evidence that pain may act as a supportive mechanism to the airway, protecting it from collapse, thus opiates were not found to have a dose relationship or group effect with obstructive sleep apnea index. Other explanations for this finding could be bias from subject selection, or the fact that subjects in the pain group were taking medications known to suppress REM sleep. Obstructive apneic events are more likely to occur during the REM sleep.

Although pain may serve a protective mechanism against obstructive sleep apnea, it does not appear to provide protection against central sleep apnea. Pain appears to actually contribute to central sleep apnea.

Like oxygen saturations, excessive daytime sleepiness in patients taking opiates was at clinically relevant (> 10) levels, but not worse than other patients with sleep disordered breathing. It could be that excessive daytime sleepiness (somnolence) reported by patients in clinical trials of opiates could be due to the development of central sleep apnea although this study was not designed to address this question.

Evidence that has been published while this study was under way infers that opiates may be associated with a form of sleep disordered breathing called complex or mixed apnea (Walker et al., 2007; L. R. Webster et al., 2008). Complex apnea presents with mixed apneic events that appears not to respond to conventional treatment of continuous positive airway pressure in case reports. The current study originally focused on only central or obstructive sleep apnea. To address the issue of complex sleep apnea, post hoc analysis of mixed apnea events was performed. Patients taking opiates did not have more complex apneic events, nor was there an opiate dose relationship with mixed apneic events.

Regardless of the mechanism, it seems prudent that clinicians be made aware that some patients may be at risk of adverse effects of using opiates, especially at higher doses. Patients with OSA may be especially at risk of adverse events of using opiates especially if the OSA is undiagnosed and/or untreated. Having knowledge of the risk factors for sleep disordered breathing will allow clinicians to recognize who may be at added risk of adverse effects when using opiate medications.

Risk Factors for Sleep Disordered Breathing

Risk factors associated with the dependent variables in this study are demonstrated in table 18. The directions of predictions were found to coincide with previous evidence and to be clinically appropriate. Known risk factors for OSA are male gender, obesity (BMI > 30), older age, neck circumference > 16 inches, retrognathia, and narrowed airway (Hiestand et al., 2006; Ryan et al., 2007; Tsai et al., 2003; Young, Skatrud, & Peppard, 2004). As with previous evidence, in this study risk factors for OSA were older age, male gender, and higher BMI. Corroborating with the risk factors for OSA, the predictors for higher oxygen saturations were in agreement with past research findings of younger age, female gender, and lower BMI. Consistent with previous evidence, BMI was found to be a risk factor for OSA but not CSA. Presence of anatomical abnormalities and number of co-morbid conditions were not predictors of SDB.

Since excessive daytime sleepiness is known to be a sign of SDB, it seems likely that predictors for excessive daytime sleepiness would be the same as predictors of SDB. The findings from this study did not reveal that finding. Actually, excessive daytime sleepiness did not differ between groups, nor were risk factors found to be predictors.

Excessive daytime sleepiness and fatigue are two common reasons for referral for a sleep evaluation which may be the reason for lack of variance on this variable.

In future studies, precise measurement of neck circumference, retrognathia, and airway passage are likely to provide variance thus, better predictive ability. The comorbidities variable also lacked variance. Forty five percent of the subjects reported having hypertension, 35% of the subjects were taking antihypertensive medications and 82% of the subjects had signs of anatomical abnormalities typical of OSA documented in their medical record. Both of these risk factors are well known to providers and are most likely the criteria used to refer their patients for sleep studies. Both were also measured categorically, which decreases variance. A study using a random sample of chronic pain patients as opposed to potentially sleep disordered patients is recommended to address this issue.

Risk Factors for Pain

Age, gender (being female) and obesity are predictors of having a painful condition (Chiu et al., 2006; Lacey, Lewis, & Sim, 2005; National Center for Health Statistics, 2006; Leboeuf, et al. 1999; Marcus et al., 2004). The results of this study coincide with previous literature; age is a significant predictor of having a painful condition. Increased number of co-morbid conditions also was a significant predictor of pain. Interestingly, obesity, was not found to be significant predictor of pain. This could be the result of selection bias of our sample, as most of the subjects in this study were obese.

Pain and central sleep apnea share common risk factors of older age and female gender. Comparing the risk factors for pain with the risk factors for sleep disordered

breathing informs us of the need to educate our patients with pain on their added risk for sleep disordered breathing and how to access proper diagnosis and treatment for the disorder. Additionally, clinicians in the in-patient setting could use this information to screen for patients who may be at added risk of adverse respiratory events related to the use of opiates for acute pain.

Chronic Pain, Opiates and Sleep Continuity

Chronic pain patients are known to wake up more frequently than patients without pain (National Sleep Foundation, 2007; Bair et al., 2003). Knowing that opiates are associated with CSA and, that patients with CSA are likely to experience awakenings due to hypoxia and hypercapnia it seems plausible that patients with pain and on opiates would wake up more frequently than patients without pain or opiates. In this study, there was not an opiate dose relationship nor a group difference with number of awakenings, total sleep time, minutes to get to sleep, or sleep efficiency. However, subjects in this study overall experienced poor sleep continuity.

Chronic Pain, Opiates and Sleep Architecture

Since subjects in this study frequently woke from sleep, it is likely that they would present with decreased percent of the deeper stages of sleep (stage 3/4) and REM sleep. In this study, subjects whether they had pain or not and if they had pain, whether or not they were taking opiates did not differ on percent of stage 3/4 sleep. All subjects on average were clinically deprived of the deeper and more restorative stages of sleep. The average percent of stage 3/4 sleep was 6.8 (sd 9) with normal requirements 20-25% of total sleep time. Interestingly, there was a dose related relationship between opiate and percent of stage 3/4 sleep. A patient on 100 mg of morphine equivalent opiate could be

expected to have 1.1 percent more stage 3/4 sleep than a patient not taking opiates. The clinical relevance of 1.1 percent of stage 3/4 sleep is unknown but in general it is thought that the higher percent of the deep stages of sleep, the better. But as the group means did not differ, the dose response is not likely to have clinical relevance.

Many medications are known to suppress REM sleep, opiates included. This study, as hypothesized, found that subjects taking opiates had significantly less 0% - 28% (M 14%) REM sleep than subjects with pain not taking opiates 9% - 29% (M 19%). Moreover, there was no difference in percent of REM sleep between patients with and without pain. REM deprivation (< 20% of total sleep time) is commonly found in patients with sleep disordered breathing and is thought to contribute to the increased incidence of mood disturbance also commonly found in patients with sleep disordered breathing. Patients taking opiates appear to be at added risk of REM deprivation.

As stages of sleep are reported in percent of total sleep time, it is logical that if REM and stage 3/4 sleep are decreased then stage 1 and/or stage 2 percent of sleep will increase. In this study subjects taking opiates for pain had significantly higher percent of stage 2 sleep than other subjects with pain. And subjects without pain had more stage 1 sleep than patients with pain. Increased percentage in the lighter stages of sleep in itself is unlikely to have clinical relevance.

Pain and Sleep Disordered Breathing.

Acute pain is known to stimulate respirations (Glynn, Lloyd, & Folkhard, 1981). It could be hypothesized that patients with pain would be less likely to exhibit sleep disordered breathing. According to this study, central apneic events increase as pain intensity increases although the additional variance added (1.3%) by pain intensity was

small compared to the variance (16.7%) contributed by opiate dose. This was thought to be the direct result of patients with pain more likely to be taking opiate medications. Post Hoc analysis controlling for opiate dose was performed and discredited this theory. Pain itself is associated with central apneic events. More research is needed in this area as comparisons between groups did not reveal significant central sleep apnea in the pain group.

Interestingly, despite prior evidence that opiates decrease pharyngeal tone, patients taking opiates were not found to have increased severity of obstructive sleep apnea. In fact the opposite was found. Theoretically, it seems logical that pain could serve a protective role by increasing pharyngeal tone thus negating the effects of opiates on the airway. And indeed, after controlling for opiate dose, the higher the pain intensity, the lower the OAI.

Study Limitations

As this was an unfunded dissertation study, data from a convenience sample was acquired. This sample, although it provided important evidence, left out an important segment of the chronic pain population. Patients with chronic pain on stable doses of opiates and not meeting the criteria for sleep disordered breathing for the most part were not included in the recruitment strategy.

This sample was also affected by a small percentage of patients that had such severe SDB that their PSG procedure was converted to a split night so they could immediately provide treatment. This small percentage of patients included six potential subjects that were taking opiates for pain.

Scoring polysomnographic records requires skill and experience. Despite similar training of the techs and inter-rater reliability testing at the labs, it is likely that variability exists among the six techs that scored records for this study. This variability, random error in measurement, is inherent to the interpreting of the waveforms. Not all apneic events are absolute, body movement, timing of sleep stage change with breath initiation, etc can present with waveforms that deviate from the typical appearing waveform. Thus the interpretation can be somewhat subjective. As the sample in this study was 419, this limitation should have limited effect on the results of this study.

Objective measurement of opiate dose would provide a more precise measurement than subjective report. In future studies, using serum opiate levels would offer precise measurement. Serum opiate levels will also allow discovery of individual differences in absorption and peak effect on respiration and sleep disruption.

Future Research

This descriptive study explored correlation relationships. Further studies are needed to determine causal relationships, individual differences in the development of tolerance to opiates, clinical relevance, and appropriate treatment. Other considerations not covered by this study are: differences between the opiate medications, comparisons of sleep and breathing between methadone maintenance patients and chronic pain patients, further delineation of type of sleep disordered breathing comparing NREM and REM, more precise measures of intermittent hypoxia, effects of other medication being taken concurrently, and time spent at levels considered hypoxic.

This study provides evidence to support a prospective long term natural history study of chronic pain patients from the initiation of opiate medications for a course of 3-5

years. Primary measures would be health outcome related with special attention to health outcomes such as sleep, respiratory function, immune function, cardiac disease, hypertension, weight gain, glucose metabolism, and mood. Further research is also needed in the area of tolerance to the adverse effects of opiates. Factors in question are time of development, changes at the cellular level, and genetic/individual differences with respect to medication and timing of tolerance.

Conclusion

Pain is often undertreated due to providers' fears of using opiates for chronic pain. Unfortunately, the results of this study could accentuate these fears. This study was performed to provide further evidence on how to safely manage pain with opiates. Opiates have the potential to improve quality of life and function when used appropriately. Little is known about the respiratory depressive effects of opiates, especially when used for chronic pain. Clinicians should be aware that some patients are at risk for sleep disordered breathing when using opiates. Sleep disordered breathing is treatable; and if present should not be an obstacle for safe and effective management of pain using opiates.

References

Academy of Sleep Medicine. (2007). *AASM clinical practice parameters & review papers*. Westchester, IL: Academy of Sleep Medicine.

Alajmi, M., Mulgrew, A. T., Fox, J., Davidson, W., Schulzer, M., Mak, E., et al. (2007). Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: A meta-analysis of randomized controlled trials. *Lung, 185*(2), 67-72.

Alam, I., Mahmud, S., Ackroyd, R., & Baxter, J. N. (2006). Laparoscopic gastric bypass in a patient with malrotation of the intestine. *Obesity Surgery: The Official Journal of the American Society for Bariatric Surgery and of the Obesity Surgery Society of Australia and New Zealand, 16*(6), 777-779.

American Geriatrics Society. (2002). Persistent pain management guideline. *Journal of Pain & Palliative Care Pharmacotherapy, 16*(4), 127-129.

American Pain Foundation. (2005). *2004 Americans living with pain survey.* Retrieved 1/10, 2007, from http://www.painfoundation.org/page.asp?file=Library/PainSurveys.htm

American Pain Society. (1999). *Principles of analgesic use in the treatment of acute pain and cancer pain* (4th ed.). Glanview, IL: American Pain society.

American Pain Society (Ed.). (2002). *Guidelines for the management of pain in osteoarthiritis, rheumatoid arthritis, and juvenile chronic arthritis.* Glenview, IL: Author.

Amin, S., Niu, J., Guermazi, A., Grigoryan, M., Hunter, D. J., Clancy, M., et al. (2007). Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Annals of the Rheumatic Diseases, 66*(1), 18-22.

Anch, A. M., Lue, F. A., MacLean, A. W., & Moldofsky, H. (1991). Sleep physiology and psychological aspects of the fibrositis (fibromyalgia) syndrome. *Canadian Journal of Psychology, 45*(2), 179-184.

Arkinstall, W., Sandler, A., Goughnour, B., Babul, N., Harsanyi, Z., & Darke, A. C. (1995). Efficacy of controlled-release codeine in chronic non-malignant pain: A randomized, placebo-controlled clinical trial. *Pain, 62*(2), 169-178.

Athanasos, P., Smith, C. S., White, J. M., Somogyi, A. A., Bochner, F., & Ling, W. (2006). Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. *Pain, 120*(3), 267-275.

Ayonrinde, O. T., & Bridge, D. T. (2000). The rediscovery of methadone for cancer pain management. *The Medical Journal of Australia, 173*(10), 536-540.

Babu, A. R., Herdegen, J., Fogelfeld, L., Shott, S., & Mazzone, T. (2005). Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Archives of Internal Medicine, 165*(4), 447-452.

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: A literature review. *Archives of Internal Medicine, 163*(20), 2433-2445.

Benca, R. M. (2005). Diagnosis and treatment of chronic insomnia: A review. *Psychiatric Services (Washington, D.C.), 56*(3), 332-343.

Borgbjerg, F. M., Nielsen, K., & Franks, J. (1996). Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: A controlled study in human volunteers. *Pain, 64*(1), 123-128.

Branco, J., Atalaia, A., & Paiva, T. (1994). Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. *The Journal of Rheumatology, 21*(6), 1113-1117.

Buckhalt, J. A., El-Sheikh, M., & Keller, P. (2007). Children's sleep and cognitive functioning: Race and socioeconomic status as moderators of effects. *Child Development, 78*(1), 213-231.

Budhiraja, R., Sharief, I., & Quan, S. F. (2005). Sleep disordered breathing and hypertension. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine, 1*(4), 401-404.

Caldwell, J. R., Hale, M. E., Boyd, R. E., Hague, J. M., Iwan, T., Shi, M., et al. (1999). Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. *The Journal of Rheumatology, 26*(4), 862-869.

Caldwell, J. R., Rapoport, R. J., Davis, J. C., Offenberg, H. L., Marker, H. W., Roth, S. H., et al. (2002). Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *Journal of Pain and Symptom Management, 23*(4), 278-291.

Carskadon, M. A., & Dement, W. (2005). Normal human sleep: An overview. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 13-23). Philadelphia: Elsevier Saunders.

Center for Disease Control. (2005). *Increase in poisoning deaths caused by non-illicit drugs -- Utah, 1991-2003* No. 54). Washington, DC: Center for Disease Control. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5402a1.htm

Center for Disease Control. (2007). *U. S. obesity trends 1983 -2005.* Retrieved July 22, 2007, from http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Chapman, C. R., & Okifuji, A. (2004). Pain: Basic mechanisms and conscious experience. In R. H. Dworkin, & W. S. Breitbart (Eds.), *Psychosocial aspects of pain: A handbook for health care providers* (pp. 3-28). Seattle: WA: IASP Press.

Chaput, J. P., Despres, J. P., Bouchard, C., & Tremblay, A. (2007). Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. *Obesity, 15* (1), 253-261.

Cherny, N. (2002). Part A: Pain. In A. M. Berger, R. K. Portenoy & D. E. Weissman (Eds.), *Principles and practice of palliative care and supportive oncology* (2nd ed., pp. 3-52). Philadelphia: Lippincott Williams & Wilkins.

Chiu, T. W., Lau, K. T., Ho, C. W., Ma, M. C., Yeung, T. F., & Cheung, P. M. (2006). A study on the prevalence of and risk factors for neck pain in secondary school teachers. *Public Health, 120*(6), 563-565.

Chokroverty, S. (1999). Physiology changes in sleep. In S. Chokroverty (Ed.), *Sleep disorders medicine: Basic science, technical considerations, and clinical aspects* (2nd ed., pp. 95-120). Boston: Butterworth Heinemann.

Cohen, A. D., Ofek-Shlomai, A., Vardy, D. A., Weiner, Z., & Shvartzman, P. (2006). Depression in dermatological patients identified by the mini international neuropsychiatric interview questionnaire. *Journal of the American Academy of Dermatology, 54*(1), 94-99.

Cowan, D. T., Wilson-Barnett, J., Griffiths, P., Vaughan, D. J., Gondhia, A., & Allan, L. G. (2005). A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Medicine (Malden, Mass.), 6*(2), 113-121.

Cox, B. M. (1991). Molecular and cellular mechanisms in opioid tolerance. In A. I. Basbaum, & J. M. Besson (Eds.), *Towards a new pharmacotherapy of pain* (pp. 137-155). Hoboken, NJ: John Wiley & Sons, Ltd.

Dahan, A., Romberg, R., Teppema, L., Sarton, E., Bijl, H., & Olofsen, E. (2004). Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. *Anesthesiology, 101*(5), 1201-1209.

Dahan, A., & Teppema, L. J. (2003). Influence of anaesthesia and analgesia on the control of breathing. *British Journal of Anaesthesia, 91*(1), 40-49.

Dimsdale, J. E., Norman, D., DeJardin, D., & Wallace, M. S. (2007). The effect of opioids on sleep architecture. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine, 3*(1), 33-36.

Dixon, J. B., Schachter, L. M., & O'Brien, P. E. (2005). Polysomnography before and after weight loss in obese patients with severe sleep apnea. *International Journal of Obesity (2005), 29*(9), 1048-1054.

Drewes, A. M., Nielsen, K. D., Arendt-Nielsen, L., Birket-Smith, L., & Hansen, L. M. (1997). The effect of cutaneous and deep pain on the electroencephalogram during sleep--an experimental study. *Sleep, 20*(8), 632-640.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., et al. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain, 113*(1-2), 9-19.

Eisenberg, E., McNicol, E. D., & Carr, D. B. (2005). Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. *JAMA : The Journal of the American Medical Association, 293*(24), 3043-3052.

Farney, R. J., Walker, J. M., Cloward, T. V., & Rhondeau, S. (2003). Sleep-disordered breathing associated with long-term opioid therapy. *Chest, 123*(2), 632-639.

Fink, B. R. (1961). Influence of cerebral activity in wakefulness on regulation of breathing. *Journal of Applied Physiology, 16*, 15-20.

Flemons, W. W., Whitelaw, W. A., Brant, R., & Remmers, J. E. (1994). Likelihood ratios for a sleep apnea clinical prediction rule. *American Journal of Respiratory and Critical Care Medicine, 150*(5 Pt 1), 1279-1285.

Fukuda, K. (2005). Intravenous opioid anesthetics. In R. D. Miller (Ed.), *Miller's anesthesia* (6th ed., pp. 379-439). Philadelphia: Elsevier.

Fukuda, K. (2000). Scientific principles; intravenous opioid anesthetics. In R. D. Miller (Ed.), *Anesthesia* (5th ed., pp. 380-407). New York: Churchhill Livingstone.

Gallagher, E. J., Bijur, P. E., Latimer, C., & Silver, W. (2002). Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *The American Journal of Emergency Medicine, 20*(4), 287-290.

Given, B., Given, C. W., Sikorskii, A., Jeon, S., Sherwood, P., & Rahbar, M. (2006). The impact of providing symptom management assistance on caregiver reaction: Results of a randomized trial. *Journal of Pain and Symptom Management, 32*(5), 433-443.

Glynn, C. J., Lloyd, J. W., & Folkhard, S. (1981). Ventilatory response to intractable pain. *Pain, 11*(2), 201-211.

Guilleminault, C., & Bassiri, A. (2005). Clinical features and evaluation of obsstructive sleep apnea-hypopnea syndrome and upper airway resistance syndrome. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 1043-1052). Philadelphia: Elsevier Saunders.

Gutstein, H. B., & Akil, H. (2005). Opioid analgesics. In L. Brunton, J. Lazo & K. Parker (Eds.), *Goodman and gillman's: The pharmacologic basis of therapeutics* (11th ed., pp. 547). Columbus, OH: The McGraw-Hill Companies, Inc.

Hale, M. E., Ahdieh, H., Ma, T., Rauck, R., & the Oxymorphone ER Study Group 1. (2007). Efficacy and safety of OPANA ER (oxymorphone extended release) for

relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *The Journal of Pain : Official Journal of the American Pain Society, 8*(2), 175-184.

Hargens, T. A., Nickols-Richardson, S. M., Gregg, J. M., Zedalis, D., & Herbert, W. G. (2006). Hypertension research in sleep apnea. *Journal of Clinical Hypertension (Greenwich, Conn.), 8*(12), 873-878.

Harman, K., Pivik, R. T., D'Eon, J. L., Wilson, K. G., Swenson, J. R., & Matsunaga, L. (2002). Sleep in depressed and nondepressed participants with chronic low back pain: Electroencephalographic and behaviour findings. *Sleep, 25*(7), 775-783.

Hiestand, D. M., Britz, P., Goldman, M., & Phillips, B. (2006). Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005 poll. *Chest, 130*(3), 780-786.

Hirsch, M., Carlander, B., Verge, M., Tafti, M., Anaya, J. M., Billiard, M., et al. (1994). Objective and subjective sleep disturbances in patients with rheumatoid arthritis. A reappraisal. *Arthritis and Rheumatism, 37*(1), 41-49.

Holdgate, A., Asha, S., Craig, J., & Thompson, J. (2003). Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emergency Medicine (Fremantle, W.A.), 15*(5-6), 441-446.

Horne, J. A., & Shackell, B. S. (1991). Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. *Electroencephalography and Clinical Neurophysiology, 79*(4), 271-276.

Hubain, P., Le Bon, O., Vandenhende, F., Van Wijnendaele, R., & Linkowski, P. (2006). Major depression in males: Effects of age, severity and adaptation on sleep variables. *Psychiatry Research, 145*(2-3), 169-177.

Hubain, P., Van Veeren, C., Staner, L., Mendlewicz, J., & Linkowski, P. (1996). Neuroendocrine and sleep variables in major depressed inpatients: Role of severity. *Psychiatry Research, 63*(1), 83-92.

Hudgel, D. W., & Devadatta, P. (1984). Decrease in functional residual capacity during sleep in normal humans. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 57*(5), 1319-1322.

Hudgel, D. W., Martin, R. J., Johnson, B., & Hill, P. (1984). Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 56*(1), 133-137.

International Association for the Study of Pain. (1994). In Merskey H., Bogduk N. (Eds.), *Classification of chronic pain* (2nd ed.). Seattle: IASP Press.

Irwin, M. (2002). Effects of sleep and sleep loss on immunity and cytokines. *Brain, Behavior, and Immunity, 16*(5), 503-512.

Jaffe, J. H., & Strain, E. C. (2005). Opioid-related disorders. In B. J. Sadock, & V. Sadock (Eds.), *Kaplan & sadock's comprehensive textbook of psychiatry* (pp. 1265). Philadelphia: Lippincott Williams & Wilkins. Retrieved from http://gateway.ut.ovid.com/gw2/ovidweb.cgi

Jarvik, J. G., Hollingworth, W., Heagerty, P. J., Haynor, D. R., Boyko, E. J., & Deyo, R. A. (2005). Three-year incidence of low back pain in an initially asymptomatic cohort: Clinical and imaging risk factors. *Spine, 30*(13), 1541-8; discussion 1549.

Javaheri, S. (2005). Cardiovascular disorders. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 1157-1217). Philadelphia: Elsevier Saunders.

Jensen, M. P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: A comparison of six methods. *Pain, 27*(1), 117-126.

John, U., Hanke, M., Meyer, C., Volzke, H., Baumeister, S. E., & Alte, D. (2006). Tobacco smoking in relation to pain in a national general population survey. *Preventive Medicine, 43*(6), 477-481.

Johns, M. W. (1992). Reliability and factor analysis of the Epworth sleepiness scale. *Sleep, 15*(4), 376-381.

Johns, M. W. (1994). Sleepiness in different situations measured by the Epworth sleepiness scale. *Sleep, 17*(8), 703-710.

Joranson, D. E., & Gilson, A. M. (1998). Regulatory barriers to pain management. *Seminars in Oncology Nursing, 14*(2), 158-163.

Joranson, D. E., & Gilson, A. M. (2006). Wanted: A public health approach to prescription opioid abuse and diversion. *Pharmacoepidemiology and Drug Safety, 15*(9), 632-634.

Karan, S., Voter, W., Palmer, L., & Ward, D. S. (2005). Effects of pain and audiovisual stimulation on the opioid-induced depression of the hypoxic ventilatory response. *Anesthesiology, 103*(2), 384-390.

Kay, D. C. (1975a). Human sleep and EEG through a cycle of methadone dependence. *Electroencephalography and Clinical Neurophysiology, 38*(1), 35-43.

Kay, D. C. (1975b). Human sleep during chronic morphine intoxication. *Psychopharmacologia, 44*(2), 117-124.

Kay, D. C., Pickworth, W. B., & Neider, G. L. (1981). Morphine-like insomnia from heroin in nondependent human addicts. *British Journal of Clinical Pharmacology, 11*(2), 159-169.

Keefe, F. J., Lipkus, I., Lefebvre, J. C., Hurwitz, H., Clipp, E., Smith, J., et al. (2003). The social context of gastrointestinal cancer pain: A preliminary study examining the relation of patient pain catastrophizing to patient perceptions of social support and caregiver stress and negative responses. *Pain, 103*(1-2), 151-156.

Kivitz, A., Ma, C., Ahdieh, H., & Galer, B. S. (2006). A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clinical Therapeutics, 28*(3), 352-364.

Kuivalainen, L., Ryhanen, A., Isola, A., & Merilainen, P. (1998). Sleep disturbances affecting hospital patients. [Potilaan nukkuminen sisatautien ja kirurgian osastolla] *Hoitotiede, 10*(3), 134-143.

Kushida, C. A., Littner, M. R., Morgenthaler, T., Alessi, C. A., Bailey, D., Coleman, J.,Jr, et al. (2005). Practice parameters for the indications for polysomnography and related procedures: An update for 2005. *Sleep, 28*(4), 499-521.

Lacey, R. J., Lewis, M., & Sim, J. (2005). The relationship between hand paraesthesia and occupational factors: Results from a population study. *Rheumatology (Oxford, England), 44*(10), 1287-1293.

Ladd, L. A., Kam, P. C., Williams, D. B., Wright, A. W., Smith, M. T., & Mather, L. E. (2005). Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypoxaemic conditions. *British Journal of Clinical Pharmacology, 59*(5), 524-535.

Laferriere, A., Colin-Durand, J., & Moss, I. R. (2005). Ontogeny of respiratory sensitivity and tolerance to the mu-opioid agonist fentanyl in rat. *Brain Research.Developmental Brain Research, 156*(2), 210-217.

Lake, J. K., Power, C., & Cole, T. J. (2000). Back pain and obesity in the 1958 british birth cohort. cause or effect? *Journal of Clinical Epidemiology, 53*(3), 245-250.

Lalley, P. M. (2003). Mu-opioid receptor agonist effects on medullary respiratory neurons in the cat: Evidence for involvement in certain types of ventilatory disturbances. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology, 285*(6), R1287-304.

Langford, R., McKenna, F., Ratcliffe, S., Vojtassak, J., & Richarz, U. (2006). Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: A randomized, placebo-controlled trial. *Arthritis and Rheumatism, 54*(6), 1829-1837.

Lavigne, G., Zucconi, M., Castronovo, C., Manzini, C., Marchettini, P., & Smirne, S. (2000). Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems. *Pain, 84*(2-3), 283-290.

Leboeuf-Yde, C., Kyvik, K. O., & Bruun, N. H. (1999). Low back pain and lifestyle. part II--obesity. information from a population-based sample of 29,424 twin subjects. *Spine, 24*(8), 779-83; discussion 783-4.

Leino, K., Mildh, L., Lertola, K., Seppala, T., & Kirvela, O. (1999). Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anaesthesia, 54*(9), 835-840.

Lewis, S. A., Oswald, I., Evans, J. I., & Akindele, M. O. (1970). Heroin and human sleep. *Electroencephalography and Clinical Neurophysiology, 28*(4), 429.

Lineberger, M. D., Carney, C. E., Edinger, J. D., & Means, M. K. (2006). Defining insomnia: Quantitative criteria for insomnia severity and frequency. *Sleep, 29*(4), 479-485.

Maier, C., Hildebrandt, J., Klinger, R., Henrich-Eberl, C., Lindena, G., & MONTAS Study Group. (2002). Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS). *Pain, 97*(3), 223-233.

Marcus, D. A. (2004). Obesity and the impact of chronic pain. *The Clinical Journal of Pain, 20*(3), 186-191.

Markenson, J. A., Croft, J., Zhang, P. G., & Richards, P. (2005). Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *The Clinical Journal of Pain, 21*(6), 524-535.

McCracken, L. M., & Iverson, G. L. (2001). Predicting complaints of impaired cognitive functioning in patients with chronic pain. *Journal of Pain and Symptom Management, 21*(5), 392-396.

McNicol, E., Horowicz-Mehler, N., Fisk, R. A., Bennett, K., Gialeli-Goudas, M., Chew, P. W., et al. (2003). Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. *The Journal of Pain : Official Journal of the American Pain Society, 4*(5), 231-256.

Menefee, L. A., Cohen, M. J., Anderson, W. R., Doghramji, K., Frank, E. D., & Lee, H. (2000). Sleep disturbance and nonmalignant chronic pain: A comprehensive review of the literature. *Pain Medicine (Malden, Mass.), 1*(2), 156-172.

Menefee, L. A., Frank, E. D., Doghramji, K., Picarello, K., Park, J. J., Jalali, S., et al. (2000). Self-reported sleep quality and quality of life for individuals with chronic pain conditions. *The Clinical Journal of Pain, 16*(4), 290-297.

Mercadante, S. (2007). Opioid titration in cancer pain: A critical review. *European Journal of Pain, 11*(8), 823-830.

Mercadante, S., & Bruera, E. (2006). Opioid switching: A systematic and critical review. *Cancer Treatment Reviews, 32*(4), 304-315.

Milgrom-Friedman, J., Penman, R., & Meares, R. (1983). A preliminary study on pain perception and tobacco smoking. *Clinical and Experimental Pharmacology & Physiology, 10*(2), 161-169.

Mitler, M., Poceta, S., & Bigby, B. (1999). Sleep scoring technique. In S. Chokroverty (Ed.), *Sleep disorders medicine: Basic science, technical considerations, and clinical aspects* (2nd ed., pp. 245-262). Boston: Butterworth Heinemann.

Montplaisir, J., Allen, R., Walters, A., & Ferini-Strambi, L. (2005). Neurologic disorders. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 839-852). Philadelphia: Elsevier Saunders.

Moore, R. A., & McQuay, H. J. (2005). Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomized trials of oral opioids. *Arthritis Research & Therapy, 7*(5), R1046-51.

Moreno, C. R., Louzada, F. M., Teixeira, L. R., Borges, F., & Lorenzi-Filho, G. (2006). Short sleep is associated with obesity among truck drivers. *Chronobiology International, 23*(6), 1295-1303.

Morin, C. M., Gibson, D., & Wade, J. (1998). Self-reported sleep and mood disturbance in chronic pain patients. *The Clinical Journal of Pain, 14*(4), 311-314.

Moulin, D. E., Iezzi, A., Amireh, R., Sharpe, W. K., Boyd, D., & Merskey, H. (1996). Randomised trial of oral morphine for chronic non-cancer pain. *Lancet, 347*(8995), 143-147.

National Center for Health Statistics. (2006). *Health, United States, 2006 with chartbook on trends in health of Americans* No. 76-641496). Hyattsville, MD: US Government Printing Office.

National Sleep Foundation. (2007). *2007 sleep in america poll*. Washington: National Sleep Foundation. Retrieved from http://www.sleepfoundation.org/site/c.huIXKjM0IxF/b.2574229/k.14DA/2007_Sleep_in_America_Poll.htm

Netzer, N. C., Stoohs, R. A., Netzer, C. M., Clark, K., & Strohl, K. P. (1999). Using the berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Annals of Internal Medicine, 131*(7), 485-491.

Newman, A. B., Foster, G., Givelber, R., Nieto, F. J., Redline, S., & Young, T. (2005). Progression and regression of sleep-disordered breathing with changes in weight: The sleep heart health study. *Archives of Internal Medicine, 165*(20), 2408-2413.

Nielsen, K. D., Drewes, A. M., Svendsen, L., Bjerregard, K., & Taagholt, S. (1994). Ambulatory recording and power spectral analysis by autoregressive modelling of

polygraphic sleep signals in patients suffering from chronic pain. *Methods of Information in Medicine, 33*(1), 76-78.

Oginska, H., & Pokorski, J. (2006). Fatigue and mood correlates of sleep length in three age-social groups: School children, students, and employees. *Chronobiology International, 23*(6), 1317-1328.

Ohayon, M. M. (2004). Interactions between sleep normative data and sociocultural characteristics in the elderly. *Journal of Psychosomatic Research, 56*(5), 479-486.

Ohayon, M. M., & Lemoine, P. (2004). Sleep and insomnia markers in the general population. [Sommeil et principaux indicateurs d'insomnie dans la population generale francaise] *L'Encephale, 30*(2), 135-140.

Palangio, M., Damask, M. J., Morris, E., Doyle, R. T.,Jr, Jiang, J. G., Landau, C. J., et al. (2000). Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. *Clinical Therapeutics, 22*(7), 879-892.

Parisi, R. A. (1999). Respiration and respiratory function: Technique of recording and evaluation. In S. Chokroverty (Ed.), *Sleep disorders medicine: Basic science, technical considerations, and clinical aspects* (2nd ed., pp. 215-221). Boston: Butterworth Heinemann.

Patanwala, A. E., Duby, J., Waters, D., & Erstad, B. L. (2007). Opioid conversions in acute care. *The Annals of Pharmacotherapy, 41*(2), 255-266.

Peloso, P. M., Bellamy, N., Bensen, W., Thomson, G. T., Harsanyi, Z., Babul, N., et al. (2000). Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *The Journal of Rheumatology, 27*(3), 764-771.

Peppard, P. E., Szklo-Coxe, M., Hla, K. M., & Young, T. (2006). Longitudinal association of sleep-related breathing disorder and depression. *Archives of Internal Medicine, 166*(16), 1709-1715.

Peppard, P. E., Young, T., Palta, M., & Skatrud, J. (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *The New England Journal of Medicine, 342*(19), 1378-1384.

Peterson, M. J., & Benca, R. M. (2006). Sleep in mood disorders. *The Psychiatric Clinics of North America, 29*(4), 1009-32; abstract ix.

Pickett, J. (2000). *The American heritage dictionary of the English language, 4th ed.* Retrieved December 02, 2004, from http://www.bartleby.com/61/94/S0469400.html

Pickworth, W. B., Neidert, G. L., & Kay, D. C. (1981). Morphinelike arousal by methadone during sleep. *Clinical Pharmacology and Therapeutics, 30*(6), 796-804.

Pigeon, W., Park, R., & Sateia, M. (2004). Sleep and pain. In M. Lader, D. Cardinali & S. R. Pandi-Perumal (Eds.), *Sleep and sleep disorders: A neuropsychological approach* (). Austin, TX: Landes Bioscience.

Pilowsky, I., Crettenden, I., & Townley, M. (1985). Sleep disturbance in pain clinic patients. *Pain, 23*(1), 27-33.

Poitou, C., Coupaye, M., Laaban, J. P., Coussieu, C., Bedel, J. F., Bouillot, J. L., et al. (2006). Serum amyloid A and obstructive sleep apnea syndrome before and after surgically-induced weight loss in morbidly obese subjects. *Obesity Surgery : The Official Journal of the American Society for Bariatric Surgery and of the Obesity Surgery Society of Australia and New Zealand, 16*(11), 1475-1481.

Pool, G. J., Schwegler, A. F., Theodore, B. R., & Fuchs, P. N. (2007). Role of gender norms and group identification on hypothetical and experimental pain tolerance. *Pain, 129*(1-2), 122-129.

Price, D. D., Greenspan, J. D., & Dubner, R. (2003). Neurons involved in the exteroceptive function of pain. *Pain, 106*(3), 215-219.

Punjabi, N. M., & Polotsky, V. Y. (2005). Disorders of glucose metabolism in sleep apnea. *Journal of Applied Physiology (Bethesda, Md.: 1985), 99*(5), 1998-2007.

Rains, J. C., & Penzien, D. B. (2003). Sleep and chronic pain: Challenges to the alpha-EEG sleep pattern as a pain specific sleep anomaly. *Journal of Psychosomatic Research, 54*(1), 77-83.

Rasmussen, B. K. (1993). Migraine and tension-type headache in a general population: Precipitating factors, female hormones, sleep pattern and relation to lifestyle. *Pain, 53*(1), 65-72.

Rauck, R. L., Bookbinder, S. A., Bunker, T. R., Alftine, C. D., Gershon, S., de Jong, E., et al. (2007). A randomized, open-label, multicenter trial comparing once-a-day AVINZA (morphine sulfate extended-release capsules) versus twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: Improved physical functioning in the ACTION trial. *Journal of Opioid Management, 3*(1), 35-43.

Rauck, R. L., Bookbinder, S. A., Bunker, T. R., Alftine, C. D., Ghalie, R., Negro-Vilar, A., et al. (2006). A randomized, open-label study of once-a-day AVINZA (morphine sulfate extended-release capsules) versus twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for chronic low back pain: The extension phase of the ACTION trial. *Journal of Opioid Management, 2*(6), 325-8, 331-3.

Raymond, I., Ancoli-Israel, S., & Choiniere, M. (2004). Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. *Sleep Medicine, 5*(6), 551-559.

Rechtshaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. LosAngeles: UCLA Brain information Services/Brain Research Institute.

Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M. (2000). Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *The Journal of Clinical Endocrinology and Metabolism, 85*(10), 3597-3603.

Ripamonti, C., De Conno, F., Groff, L., Belzile, M., Pereira, J., Hanson, J., et al. (1998). Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: Comparison of two clinical experiences. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO, 9*(1), 79-83.

Ripamonti, C., Groff, L., Brunelli, C., Polastri, D., Stavrakis, A., & De Conno, F. (1998). Switching from morphine to oral methadone in treating cancer pain: What is the equianalgesic dose ratio? *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 16*(10), 3216-3221.

Romberg, R., Olofsen, E., Sarton, E., Teppema, L., & Dahan, A. (2003). Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers. *Anesthesiology, 99*(4), 788-798.

Ronthal, M. (2004). Neck and back pain. In M. A. Samuels (Ed.), *Manual of neurologic therapeutics* (7th ed., pp. 85). Philadelphia: Lippincott Williams & Wilkins. Retrieved from http://gateway.ut.ovid.com/gw1/ovidweb.cgi

Roth, S. H., Fleischmann, R. M., Burch, F. X., Dietz, F., Bockow, B., Rapoport, R. J., et al. (2000). Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: Placebo-controlled trial and long-term evaluation. *Archives of Internal Medicine, 160*(6), 853-860.

Ryan, S., Nolan, G., Hannigan, E., Cunningham, S., Taylor, C. T., & McNicholas, W. T. (2007). Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. *Thorax,*

Ryan, S., Taylor, C. T., & McNicholas, W. T. (2005). Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation, 112*(17), 2660-2667.

Sanders, M. H. (2005). Sleep breathing disorders. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 969-1156). Philadelphia: Elsevier Saunders.

Sandrini, G., Milanov, I., Rossi, B., Murri, L., Alfonsi, E., Moglia, A., et al. (2001). Effects of sleep on spinal nociceptive reflexes in humans. *Sleep, 24*(1), 13-17.

Schumacher, M. A., Basbaum, A. I., & Way, W. L. (2004). Opioid analgesics and antagonists. In B. G. Katzung (Ed.), *Basic & clinical pharmacology* (9th ed.,). New York: McGraw-Hill. Retrieved from http://mdl.miner.rochester.edu/mdl/mdl.cgi?categories=EBOOK

Shaw, I.R., Lavigne, G., Mayer, P., Choiniere, M. (2005). Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *SLEEP* 28(6), 677-682.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Slatkin, N. E., & Rhiner, M. (2003). Treatment of opiate-related sedation: Utility of the cholinesterase inhibitors. *The Journal of Supportive Oncology, 1*(1), 53-63.

Smith, M. T., & Haythornthwaite, J. A. (2004). How do sleep disturbance and chronic pain inter-relate? insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Medicine Reviews, 8*(2), 119-132.

Smith, M. T., Klick, B., Kozachik, S., Edwards, R. E., Holavanahalli, R., Wiechman, S., et al. (2008). Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. *Pain,*

Smith, M. T., Perlis, M. L., Park, A., Smith, M. S., Pennington, J., Giles, D. E., et al. (2002). Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *The American Journal of Psychiatry, 159*(1), 5-11.

Spiegel, K., Knutson, K., Leproult, R., Tasali, E., & Van Cauter, E. (2005). Sleep loss: A novel risk factor for insulin resistance and type 2 diabetes. *Journal of Applied Physiology (Bethesda, Md.: 1985), 99*(5), 2008-2019.

Stewart, W. F., Ricci, J. A., Chee, E., & Morganstein, D. (2003). Lost productive work time costs from health conditions in the united states: Results from the American productivity audit. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine, 45*(12), 1234-1246.

Stoermer, R., Drewe, J., Dursteler-Mac Farland, K. M., Hock, C., Mueller-Spahn, F., Ladewig, D., et al. (2003). Safety of injectable opioid maintenance treatment for heroin dependence. *Biological Psychiatry, 54*(8), 854-861.

Strobel, R. J., & Rosen, R. C. (1996). Obesity and weight loss in obstructive sleep apnea: A critical review. *Sleep, 19*(2), 104-115.

Tang, N. K., Wright, K. J., & Salkovskis, P. M. (2007). Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *Journal of Sleep Research, 16*(1), 85-95.

Taylor, V. M., Deyo, R. A., Ciol, M., Farrar, E. L., Lawrence, M. S., Shonnard, N. H., et al. (2000). Patient-oriented outcomes from low back surgery: A community-based study. *Spine, 25*(19), 2445-2452.

Teichtahl, H., Prodromidis, A., Miller, B., Cherry, G., & Kronborg, I. (2001). Sleep-disordered breathing in stable methadone programme patients: A pilot study. *Addiction (Abingdon, England), 96*(3), 395-403.

Teichtahl, H., Wang, D., Cunnington, D., Quinnell, T., Tran, H., Kronborg, I., et al. (2005). Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. *Chest, 128*(3), 1339-1347.

The Open Mind Initiative. (2006). The white paper on opioids and pain: A pan-european challenge: The european white paper on the use of opioids in chronic pain management. *Journal of Pain & Palliative Care Pharmacotherapy, 20*(3), 79-87.

Thomson Healthcare, I. (2007). *Micromedex.* Retrieved July 14, 2007, from http://www.thomsonhc.com/hcs/librarian

Tsai, W. H., Remmers, J. E., Brant, R., Flemons, W. W., Davies, J., & Macarthur, C. (2003). A decision rule for diagnostic testing in obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 167*(10), 1427-1432.

Tsai, Y. F. (2007). Gender differences in pain and depressive tendency among chinese elders with knee osteoarthritis. *Pain, 130*(1-2), 188-194.

United States Department of Justice Drug Enforcement Administration. (2006). *U. S. summary of retail drug purchases.* Retrieved March 22, 2007, from http://www.deadiversion.usdoj.gov/arcos/index.html

Unruh, A. M. (1996). Gender variations in clinical pain experience. *Pain, 65*(2-3), 123-167.

Van Cauter, E., Holmback, U., Knutson, K., Leproult, R., Miller, A., Nedeltcheva, A., et al. (2007). Impact of sleep and sleep loss on neuroendocrine and metabolic function. *Hormone Research, 67 Suppl 1*, 2-9.

Wagner, P., & West, J. (2005). Respiratory physiology. In R. Mason, J. Murray, B. Braoddus & J. Nadel (Eds.), *Mason: Murray & nadel's textbook of respiratory medicine* (4th ed., pp. 51). St. Louis: W.B. Saunders. Retrieved from http://www.mdconsult.com/das/book/body/77376303-3/0/1288/1.html?tocnode=51469937&fromURL=1.html

Walczak, T., & Chokroverty, S. (1999). Electroencephalography, electromyography, and electro-oculography: General principles and basic technology. In S. Chokroverty (Ed.), *Sleep disorders medicine: Basic science, technical considerations, and clinical aspects* (2nd ed., pp. 175-214). Boston: Butterworth Heinemann.

Waldhoer, M., Bartlett, S. E., & Whistler, J. L. (2004). Opioid receptors. *Annual Review of Biochemistry, 73*, 953-990.

Walker, J. M., Farney, R. J., Rhondeau, S. M., Boyle, K. M., Valentine, K., Cloward, T. V., et al. (2007). Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine, 3*(5), 455-461.

Wang, D., Teichtahl, H., Drummer, O., Goodman, C., Cherry, G., Cunnington, D., et al. (2005). Central sleep apnea in stable methadone maintenance treatment patients. *Chest, 128*(3), 1348-1356.

Webster, L., Andrews, M., & Stoddard, G. (2003). Modafinil treatment of opioid-induced sedation. *Pain Medicine (Malden, Mass.), 4*(2), 135-140.

Webster, L. R., Choi, Y., Desai, H., Webster, L., & Grant, B. J. (2008). Sleep-disordered breathing and chronic opioid therapy. *Pain Medicine (Malden, Mass.), 9*(4), 425-432.

White, D. P. (2005). Central sleep apnea. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (). Philadelphia: Elsevier Saunders.

Wild, S. H., & Byrne, C. D. (2006). ABC of obesity. risk factors for diabetes and coronary heart disease. *BMJ (Clinical Research Ed.), 333*(7576), 1009-1011.

Winkelstein, B. A. (2004). Mechanisms of central sensitization, neuroimmunology & injury biomechanics in persistent pain: Implications for musculoskeletal disorders. *Journal of Electromyography and Kinesiology : Official Journal of the International Society of Electrophysiological Kinesiology, 14*(1), 87-93.

Winterstein, A. G., Hatton, R. C., Gonzalez-Rothi, R., Johns, T. E., & Segal, R. (2002). Identifying clinically significant preventable adverse drug events through a hospital's database of adverse drug reaction reports. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists, 59*(18), 1742-1749.

Winterstein, A. G., Sauer, B. C., Hepler, C. D., & Poole, C. (2002). Preventable drug-related hospital admissions. *The Annals of Pharmacotherapy, 36*(7-8), 1238-1248.

Wittig, R. M., Zorick, F. J., Blumer, D., Heilbronn, M., & Roth, T. (1982). Disturbed sleep in patients complaining of chronic pain. *The Journal of Nervous and Mental Disease, 170*(7), 429-431.

Woolf, C. J. (2007). Central sensitization: Uncovering the relation between pain and plasticity. *Anesthesiology, 106*(4), 864-867.

Yamakawa, K., Tsai, C. K., Haig, A. J., Miner, J. A., & Harris, M. J. (2004). Relationship between ambulation and obesity in older persons with and without low back pain. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity, 28*(1), 137-143.

Yee, B., Liu, P., Phillips, C., & Grunstein, R. (2004). Neuroendocrine changes in sleep apnea. *Current Opinion in Pulmonary Medicine, 10*(6), 475-481.

Young, T., & Peppard, P. E. (2005). Clinical presentation of OSAS: Gender does matter. *Sleep, 28*(3), 293-295.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine, 165*(9), 1217-1239.

Young, T., Peppard, P. E., & Taheri, S. (2005). Excess weight and sleep-disordered breathing. *Journal of Applied Physiology (Bethesda, Md.: 1985), 99*(4), 1592-1599.

Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. *JAMA : The Journal of the American Medical Association, 291*(16), 2013-2016.

Appendix A. Sleep Disorders Questionnaire (Site A & B)

Medical Problems-Section I Have you ever been told you have:	yes	no
High blood pressure		
(if yes, circle please) Heart disease, heart attack, or irregular heart rhythm		
(if yes, circle please) Stroke, serious head injury, seizures		
(if yes, circle please) Lung disease such as emphysema, chronic obstructive lung disease, asthma		
Diabetes or high blood sugars		
Cancer Location on your body _____		
Thyroid disease		
(if yes, circle please) Multiple sclerosis, Lou Gehrig's Disease, Myasthenia Gravis, Myotonic Dystrophy		
Liver disease		
Kidney disease		
Chronic pain (lasting longer than 6 months)?		
If you have chronic pain, where on your body do you have pain? _____		
What is the cause of your pain? _____		
Do you have any medical problems not listed above? If so, please list _____		
Have you ever had surgery on your throat or nose? If so, what type of surgery? _____		
Do you smoke? If so, how many cigarettes a day _____		
Did you quit smoking within the past 3 months?		
How many alcoholic drinks do you consume? Please check the correct box. 0 1-3 a month 1-3 a week 4-7 a week 8-14 a week more than 14 a week		
Did you quit drinking within the past 3 months?		
Depression screen-Section II	yes	no
Have you been depressed or down most of the day, nearly every day for the past two weeks?		
In the past two weeks, have you been much less interested in most things you used to enjoy most of the time?		

Pain Screen – Section III	yes	no
Do you have pain most days?		
Do you take pain medications? If so, please list on the next sheet		

How long has pain been a problem for you? _____

Mark in the box beside the number that describes how much on average pain interferes with your sleep.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does not interfere — Completely interferes

Please rate your pain by marking the box beside the number that best describes your pain on average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Please rate your pain by marking the box beside the number that best describes your pain right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Excessive Daytime Sleepiness -- Section IV

Over the past month, how likely were you to doze or fall asleep in the following situations? Please enter the number on the line below.

Chance of falling to sleep

_____Sitting and reading

_____Sitting and talking to someone

_____Sitting quietly after lunch without alcohol

_____Watching TV

_____Lying down to rest in the afternoon when circumstance permits

_____Sitting inactive in a public place (e.g. theater or meeting)

_____As a passenger in a car for an hour without break

_____In a car stopped for a few minutes stopped in traffic

Medication use – Section V				
List ALL medications including over the counter medications, herbals and the ones you take only if needed.	Strength of pill (dose)	Number of pills taken TODAY	How many *months* ago did you start taking this medication?	How many days a week do you actually take this medication?
Aciphex	10mg	2	18	6

Have you stopped taking any medications in the past 3 months? If so, what?_____

If female, when was your last menstrual period? _____
Which of these groups would you say best describes your racial background?

AMERICAN INDIAN/ALASKA NATIVE 1
ASIAN/PACIFIC ISLANDER 2
BLACK, NOT HISPANIC 3
CAUCASIAN 4
HISPANIC 5
BIRACIAL BOTH BLACK/WHITE 6
BIRACIAL OTHER (SPECIFY)_____ 7
OTHER (SPECIFY)_____ 8

Which of these groups describes your ethnic background?

HISPANIC OR LATINO..... ....
1
NOT HISPANIC OR LATINO 2

If we have further questions would it be ok if we called you? _____ yes _____ no
If yes, what phone number and time would be best for you?
Days Phone number _____ Evenings Phone number _____
Thank you,
Carla Jungquist, RN, FNP, doctoral student

Pages 154 – 161, Appendix B, removed and permanently restricted at the request of the author.

Reason: copyrighted material.

Appendix C. Brochure for Site B

Thank you for your interest in this research study.

If you have any questions please feel free to email or page

Carla Jungquist, RN,
Doctoral Candidate

University of Rochester
School of Nursing
Rochester, NY 14642
Pager: 585-220-7986
Carla_Jungquist@URMC.Rochester.edu

Unity Sleep Disorders Center

and

University of Rochester School of Nursing

Invite you to participate in a Research Study

"Chronic Pain, Sleep, and Medications Used for Pain"

Chronic Pain, Sleep, and Medications

Overview

Dr. Israel and the other providers at the Unity Sleep Disorders Center are assisting a nursing doctoral student with her dissertation project.

Carla Jungquist, the student is doing research to learn more about how chronic pain and medications used for pain affect sleep and breathing.

We are recruiting patients with and without pain for this study.

If you decide to participate, you will be asked to:

1. Fill out a questionnaire the night of your sleep study.
2. Allow the investigators access to the data from your sleep study and medical record.

At no time will your name, birth date or other identifying information be attached to the results of this study. Your data will be de-identified.

What's the next step?

On the night of your sleep study:

1. Sign the consent
2. Fill out the questionnaire

Appendix D. Letter of Introduction to Study for Potential Subjects

November 5, 2007

Dear Potential Participant:

The physicians at the Sleep Disorders Center are assisting a nursing doctoral student with her dissertation project. Carla Jungquist, the student is doing research to learn more about how chronic pain and the medications used for pain effect sleep and your breathing. I am writing to ask if you would participate in this research project. You do not have to have pain or be on medications to participate.

If you decide to participate in this study you will be asked to fill out the enclosed questionnaire and allow the investigators access to your medical record and data from your sleep study. The results of the study will be published as part of her dissertation as well as in professional journals. At no time will your name, birth date or other identifying information be attached to the results of the study. Your data will be de-identified.

We hope you will be interested in participating. You can be assured that the evaluation of and care for your sleep problem will be the highest standard of care whether or not you decide to participate.

The consent form and questionnaire are enclosed. Please feel free to read over the consent form that explains the study in closer detail. If you would like to participate, please fill out the questionnaire and return it to us the night of your sleep study. If you have any questions about the study or how we will use your medical information, please ask us or you can page Carla Jungquist at 585-220-7986.

Thank you for considering participation in the study.

Sincerely,

Don Greenblatt, MD
Michael Yurcheshen, MD
Joseph Modrak, MD

Appendix E. Data Collection Instrument

CODING SHEET	YES=1	NO=0	Coding
1. Signed Consent/literate in English?		STOP	
2. Age >21 years		STOP	
3. Did the patient have a PSG?		STOP	
4. Acute pain problem?	STOP		
5. Methadone for addiction?	STOP		
6. Surgical procedure for sleep apnea?	STOP		
7. Was the patient diagnosed with narcolepsy?	STOP		
8. Does the subject meet the criteria for chronic pain a. Chronic Pain lasting > 6 mos. (section I) b. Pain reported in section III			
9. Etiology of pain a. Disease -1 b. Accidental injury -2 c. Cancer -3 d. Idiopathic -4 e. Unknown -5			
10. Mechanism of pain a. Somatic -1 b. Visceral -2 c. Neuropathic -3 d. Unknown -4			
11. Does the subject meet the criteria for opiate use? a. Do you take meds for pain (section III) b. Opiate listed in section V			
12. Pain interferes with your sleep (0-10)			
13. Average Pain intensity (0-10)			
14. Current pain intensity (0-10)			
15. Total ESS (section IV)			
16. Opiate drug (PSG night questionnaire) a. None --- 0 b. Morphine --- 1 c. Oxycodone --- 2 d. Methadone ---- 3 e. Fentanyl ----- 4 f. Hydrocodone --- 5 g. Hydromorphone --- 6 h. Oxymorphone ---- 7 i. Codeine ----- 8 j. Propoxyphene ----- 9			
17. Opiate average daily dose (PSG questionnaire)			
18. Morphine equianalgesic dose (calculated)			

19. Pulmonary disease/smoker (section I/OV notes/CIS) a. _____ b. _____ c. _____			
20. Other Medications a. Antidepressant -- 1 b. Antireflux -- 2 c. Anticholesterol -- 3 d. Beta Blocker -- 4 e. Anticonvulsant -- 5 f. Benzodiazepine -- 6 g. Antihypertensive – 7 h. Asthma – 8 i. Estrogen – 9 j. Thyroid – 10 k. NSAID – 11 l. Tramadol – 12 m. Tylenol -13			
21. Other Medications			
22. Other Medications			
23. Other Medications			
24. Other Medications			
25. Other Medications			
26. Other Medications			
27. Number of cigarettes a day			
28. Quit smoking past 3 months			
29. Quit drinking past 3 months			
30. Cardiac disease (section I/OV notes/CIS) a. _____ b. _____ c. _____			
31. Neuromuscular disease (section I/OV notes/CIS) a. _____ b. _____ c. _____			
32. Depression – yes to both in section II			
33. Anatomical abnormalities mentioned in ROS/PE			
34. BMI (PE)			
35. Age (PE)			
36. Gender M=0 F=1 (PE)			
37. Race			
38. Ethnicity			
39. Sleep Latency to first 60 sec of sleep			
40. Latency to Stage 1			
41. Latency to Stage 2			
42. Latency to SWS			

43. TST			
44. SE			
45. REM latency from sleep onset			
46. Number of Awakenings			
47. Number of arousals			
48. Stage 1 duration			
49. Stage 1 percent of TST			
50. Stage 2 duration			
51. Stage 2 percent of TST			
52. SWS duration			
53. SWS percent of TST			
54. REM duration			
55. REM percent of TST			
56. AHI			
57. AHI (NREM)			
58. AHI (REM)			
59. Oxygen desaturation index			
60. Total limb movements			
61. LM index			
62. PLM sequences			
63. LM with arousals			
64. LM with arousals index			
65. OAI			
66. MAI			
67. CAI			
68. AI			
69. HI			
70. AHI			
71. Average duration (sec) of OA			
72. Average duration (sec) of MA			
73. Average duration (sec) of CA			
74. Average duration (sec) of All apneas			
75. Average duration (sec) of Hypopneas			
76. Average duration (sec) of all respiratory events			
77. Oxygen saturation high REM			
78. Oxygen saturation high NREM			
79. Oxygen saturation lowest REM			
80. Oxygen saturation lowest NREM			
81. Oxygen saturation mean REM			
82. Oxygen saturation mean NREM			
83. Oxygen saturation REM sd			
84. Oxygen saturation NREM sd			
85. Oxygen saturation total sd			
86. O2 saturation # of minutes below <100%			
87. O2 saturation # of minutes below <90%			

88. O2 saturation # of minutes below <85%			
89. O2 saturation # of minutes below <80%			
90. O2 saturation # of minutes below <70%			
91. O2 saturation # of minutes below <60%			
92. O2 saturation % of sleep time below <100%			
93. O2 saturation % of sleep time below <90			
94. O2 saturation % of sleep time below <85%			
95. O2 saturation % of sleep time below <80%			
96. O2 saturation % of sleep time below <70%			
97. O2 saturation % of sleep time below <60%			
98. TST Supine			
99. TST Right			
100. TST Left			
101. TST Prone			
102. RDI Supine			
103. RDI Right			
104. RDI Left			
105. RDI Prone			

Appendix F. Informed Consent (site A)

Study Title: The Relationship Among Sleep, Pain and Opiates Use

Principal Investigator: Jeanne Grace, RN, PhD.
Carla Jungquist, RN, PhD.-C
Donald Greenblatt, MD
Joseph Modrak, MD
Michael Yurcheshen, MD

Introduction:
This consent form describes a research study and what you may expect if you decide to participate. You are encouraged to read this consent form carefully and to ask the person who presents it any further questions you may have before making your decision whether or not to participate. This study is being conducted by Jeanne Grace, PhD. and Carla Jungquist, RN, PhD-C of the University of Rochester's School of Nursing.

You are being asked to participate in this study because you are being evaluated for a problem with sleeping.

Purpose of Study
The purpose of the study is to learn more about how chronic pain and the medications used for pain effect sleep and your breathing.

Description of Study Procedures
If you decide to participate in this study you will be asked to fill out a questionnaire and allow the investigators to access parts of your medical record. The questionnaire will take you about 10 minutes to fill out. The purpose of the questionnaire is to gather specific information about your medical and sleep problems as well as the medications that you take.

In addition, you will be asked to allow the investigators to use the results of your sleep evaluation and overnight sleep study for purposes of this investigation.

Number of Subjects
The number of subjects needed for this study is 1356.

Risks of Participation
This study is of minimal risk.
Benefits of Participation
Although this study is not expected to benefit you, it will help health care providers further understand what may contribute to sleep disorders.

Alternatives to Participation
You can be assured clinical care as usual if you decide not to participate.

Payments
None

Sponsor Support

The University of Rochester is not receiving payment for the support of this research study.

Confidentiality of Records and HIPAA Authorization

While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Other people may need to see the information. While they normally protect the privacy of the information, they may not be required to do so by law. Results of the research may be presented at meetings or in publications, but your name will not be used.

The federal Health Insurance Portability and Accountability Act (HIPAA) requires us to get your permission to use health information about you that we either create or use as part of the research. This permission is called an Authorization. We will use the information discovered during your evaluation with the sleep provider, and the results of your overnight sleep study along with the information you provided to us on the study questionnaire (Sleep Disorders Questionnaire).

We will use your health information to conduct this study. Health information is used to report results of research to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies and study plans. Strong Health policies let you see and copy health information after the study ends, but not until the study is completed. If you have never received a copy of the Strong Health HIPAA Notice, please ask the sleep techinician for one.

To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: The University of Rochester; and the Department of Health and Human Services.

If you decide to take part, your Authorization for this study will not expire unless you cancel (revoke) it. The information collected during your participation will be kept no longer than 7 years. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, you will also be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information as stated above.

Contact Persons

For more information concerning this research, please contact: Jeanne Grace at (585-275-8890) or Carla Jungquist at (585-220-7986).

If you have any questions about your rights as a research subject, you may contact the Human Subjects Protection Specialist at the University of Rochester Research Subjects Review Board, Box 315, 601 Elmwood Avenue, Rochester, NY 14642-8315, Telephone (585) 276-0005, for long-distance you may call toll-free, (877) 449-4441.

Voluntary Participation

Participation in this study is voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Signature/Dates

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

Study Subject: _____ Print Name

Study Subject: _____ Signature

_____ Date

Person Obtaining Consent

I have read this form to the subject and/or subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

_____ Print Name and Title

_____ Signature

_____ Date

Appendix G. Informed consent (site B)

Study Title: The Relationships among Sleep, Pain and Opiate Use

Principal Investigator: Robert Israel, M.D.
Margarita Zhavoronkova, M.D.
Alice Hoagland, PhD.
Co Investigators: Jeanne Grace, R.N., PhD.
Carla Jungquist, FNP-C

Introduction:
This consent form describes a research study and what you may expect if you decide to participate. You are encouraged to read this consent form carefully and to ask the person who presents it any further questions you may have before making your decision whether or not to participate. This study is being conducted by Robert Israel, M.D., Director of the Unity Sleep Disorders Center, Margarita Zhavoronkova, M.D., Alice Hoagland, PhD. and Jeanne Grace, RN, PhD. and Carla Jungquist, RN, PhD-C of the University of Rochester's School of Nursing.

You are being asked to participate in this study because you are being evaluated for a problem with sleeping.

Purpose of Study
The purpose of the study is to learn more about how chronic pain and the medications used for pain affect sleep and your breathing.

Description of Study Procedures

If you decide to participate in this study you will be asked to fill out a questionnaire and allow the investigators to access parts of your medical record. The questionnaire will take you about 10 minutes to fill out. The purpose of the questionnaire is to gather specific information about your medical and sleep problems as well as the medications that you take.

In addition, you will be asked to allow the investigators to use the results of your sleep evaluation and sleep studies for purposes of this investigation.

Number of Subjects
The number of subjects needed for this study is 1356.

Risks of Participation
This study is of minimal risk.

Benefits of Participation
Although this study is not expected to benefit you, it will help health care providers further understand what may contribute to sleep disorders.

Alternatives to Participation
You can be assured clinical care as usual if you decide not to participate.

Payments
None

Sponsor Support
Unity Health System and The University of Rochester are not receiving payment for the support of this research study.

Confidentiality of Records and HIPAA Authorization
The federal Health Insurance Portability and Accountability Act (HIPAA) requires study investigators to get your permission to use information about your health that is either created or used as part of the research. If you have never received a copy of the Unity Health HIPAA Notice, please ask the investigator for one.

The study investigators will make every effort to keep information we learn about you private. It is possible, however, that the protected health information disclosed with this authorization may be redisclosed by others without your authorization and may no longer be protected by the HIPAA regulation.

Information that will be used includes your medical record from the Unity Sleep Disorders Center, the report from your overnight sleep study, and your Sleep Disorders Questionnaire.

The study investigator will use your health information to conduct the study.

To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people. The Department of Health and Human Services, the Institutional Review Board at Unity Health System, the Institutional Review Board at the University of Rochester.

The information collected during your participation will be kept no longer than seven years. You have the right to receive personal information about your health for purposes of this research study at the end of the study.

Your authorization for this study will not expire unless you cancel it. You can always cancel this authorization by contacting the study investigator. If you cancel your Authorization, you will also be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others. For example, by Federal law, Unity Health System must send study information to the FDA for drug and device studies it regulates. Information that may need to be reported to FDA cannot be removed from your research records.

By signing this consent form, you give us permission to use and/or share your health information.

Contact Persons
For more information concerning this research, please contact: Robert Israel, MD (585-442-4141), Jeanne Grace at (585-275-8890) or Carla Jungquist at (585-220-7986).

If you have any questions about your rights as a research subject, you may contact the Human Subjects Protection Specialist at the Unity Health Institutional Review Board at telephone (585) 723-7056.

Voluntary Participation

Participation in this study is voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Signature/Dates

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

Study Subject: _____ Print Name

Study Subject: _____ Signature

_____ Date

Person Obtaining Consent

I have read this form to the subject and/or subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

_____ Print Name and Title

_____ Signature

_____ Date