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Objective Quantification of Daytime Sleepiness

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ABSTRACT

TITLE OF THESIS:
OBJECTIVE QUANTIFICATION OF DAYTIME SLEEPINESS

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BACKGROUND: Sleep problems affect people of all ages, race, gender, and socioeconomic classifications. Undiagnosed sleep disorders significantly and adversely impact a person's level of academic achievement, job performance, and subsequently, socioeconomic status. Undiagnosed sleep disorders also negatively impact both direct and indirect costs for employers, the national government, and the general public. Sleepiness has significant implications on quality of life by impacting occupational performance, driving ability, cognition, memory, and overall health. The purpose of this study is to describe the prevalence of daytime sleepiness, as well as other quantitative predictors of sleep continuity and quality.

METHODS: Population data from the CDC program in fatigue surveillance were used for this secondary analysis seeking to characterize sleep quality and continuity variables. Each participant underwent a standard nocturnal polysomnography and a standard multiple sleep latency test (MSLT) on the subsequent day. Frequency and chi-square tests were used to describe the sample. One-Way Analysis of Variance (ANOVA) was used to compare sleep related variables of groups with sleep latencies of <5 minutes, 5-10 minutes, and >10 minutes. Bivariate and multivariate logistic regression was used to examine the association of the sleep variables with sleep latency time.

RESULTS: The mean (SD) sleep latency of the sample was 8.8 (4.9) minutes. Twenty-four individuals had ≥1 SOREM, and approximately 50% of participants (n = 100) met clinical criteria for a sleep disorder. Individuals with shorter sleep latencies, compared to those with longer latencies reported higher levels of subjective sleepiness, had higher sleep efficiency percentages, and longer sleep times. The Epworth Sleepiness Scale, sleep efficiency percentage, total sleep time, the presence of a sleep disorder, and limb movement index were positively associated with a mean sleep latency of <5 minutes.

CONCLUSIONS: The presence of a significant percentage of sleep disorders within our study sample validate prior suggestions that such disorders remain unrecognized, undiagnosed, and untreated. In addition, our findings confirm questionnaire-based surveys that suggest a significant number of the population is excessively sleepy, or hypersomnolent. Therefore, the high prevalence of sleep disorders and the negative public health effects of daytime sleepiness demand attention. Further studies are now required to better quantify levels daytime sleepiness, within a population based sample, to better understand their impact upon morbidity and mortality. This will not only expand on our current understanding of daytime sleepiness, but it will also raise awareness surrounding its significance and relation to public health.

OBJECTIVE QUANTIFICATION OF DAYTIME SLEEPINESS

by

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- Interviewing program directors to obtain program dissemination and implementation information

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Table of Contents

List of Tables

Chapter I

Introduction

The purpose of this study is to describe the distribution of daytime sleepiness in a representative sample of a middle-aged population. Physiologic measurements can objectively measure daytime sleepiness and provide valid and reliable results. Numerous studies have described sleepiness within in a clinical population or by using subjective measures, but very few large scale epidemiologic studies exist that have quantified daytime sleepiness within the population by means of objective measures. This study will describe the prevalence of daytime sleepiness, as well as other quantitative predictors of sleep continuity and quality.

Prevalence of sleepiness in the population

A large scale epidemiologic study conducted by the National Center on Sleep Disorder Research estimates sleep problems affect 70 million people of all ages, race, gender, and socioeconomic classifications. Twenty five percent of children aged 1-5 have sleep disorders, and more than 50% of adults age 65 or above have sleep disturbances. Sixty percent, or about 40 million, of the 70 million affected are chronic disorders, and despite the wide prevalence, approximately 95% of sleep problems are undiagnosed and untreated ("Wake up America," 1993).Undiagnosed sleep disorders lead to direct and indirect costs for employers, the national government, the general public and the individual. An estimated annual amount of $15.9 billion in health care costs are related to

sleep disorders, sleep deficiency, and excessive hypersomnolence (or daytime sleepiness). In 1993, the National Center on Sleep Disorder Research projected an increase in the public health burden approximating 100 million Americans will have sleep disorders by 2050 (Roth, 1995; "Wake up America," 1993).

The recognition of sleep disturbances, sleep deprivation, and sleepiness as a public health problem is a fairly new identification. It was only 1987 when U.S. Congress passed legislation requiring the director of the National Institute of Health to coordinate a plan to conduct sleep research within Public Health Services division within the Department of Health and Human Services. The National Commission on Sleep Disorder Research was created by congress in 1988 to conduct a complete analysis on the current state of knowledge and research within sleep disorders. The resources, personnel, facilities, and social programs were examined and a long-term strategy to address sleep related problems was developed (Roth, 1995; "Wake up America," 1993).

What is sleep?

A commonly held view of sleep is that it is an interruption, or break, from the state of wakefulness. The concept that sleep is the direct opposite of wake dates back to the days of Aristotle. The necessity, cause, effect and nature of sleep have aroused conjecture in many; however, the reason why we must sleep remains an ever-present question in daily living, frequently taken for granted.

Explicit, purposeful activity occurs in the state of wakefulness. Thus a typical individual may believe the only part of life to be of any significance occurs during this time. Despite its inescapability, sleep has been socially constructed within society as

undesirable and surrounded by much negativity; wakefulness has been constructed as superior and more attractive. A vast majority of people believe themselves to be experts on the subject matter of sleep; the daily, firsthand experience fools many into thinking they are knowledgeable and confers a false sense of understanding (Kleitman, 1987).

What is normal human sleep?

Behavioral sleep is defined as, "A reversible behavioral state of perpetual disengagement from and unresponsiveness to the environment" (Carskadon & Dement, 2000). Non-rapid eye movement (NREM) sleep and REM sleep are the two recurrently cycling sleep states that constitute normal human sleep. Each sleep state is differentiated on the basis of physiology. In NREM sleep, the brain is comparatively inactive in a mobile body, and in REM sleep is an active brain (such as in wake) in a paralyzed body. NREM sleep is further broken down into Stage 1, Stage 2, and Stage 3 (or slow wave sleep). Sleep is initiated in NREM sleep, typically stage 1, and advances to deeper sleep by going through stage 2 and into slow wave sleep. The first REM interval occurs about 80-100 minutes after sleep initiation. Carskadon and Dement (2000) provide an overview of sleep in a healthy adult following a predictable sleep schedule: a) sleep begins in NREM sleep, typically in stage 1 b) the sleep cycle composed of NREM and REM sleep alternates cyclically every 90 minutes c) slow wave sleep follows sleep onset and preponderated the first third of the night d)REM sleep is connected to the 24 hour cycle of physiologic body temperature and dominates the last third of the night e) Wakefulness within sleep totals less than 5% of the night f) State 1 normally accounts for 2-5% of sleep g) Stage 2 normally accounts for 45-55% of sleep h) Stage 3 normally accounts for 3-8% of sleep i) Stage 4 normally accounts for 10-15% of sleep j) NREM sleep is

normally 75-80% of sleep k) REM sleep occurs in 4-6 distinct periods normally accounting for 20-25% of sleep.

In the field of sleep, books, articles and other works are typically prefaced by stating little is actually known and understood about sleep (Kleitman, 1987). The recognition of sleep as a public health concern is relatively new and has lead to an exponential growth in sleep research and findings in the past 25 years, but sleep research actually dates back to the 19th century.

History of sleep disorders medicine

Brain waves were discovered in 1875 by Caton, and the explanation of differences between sleep and wake states by Hans in 1930 strengthened the idea of sleep as an overall state of inactivity. A commonly held view in the early part of the 20th century was that sleep materialized as a reflexive response to a diminution of cerebral stimulation. The human electroencephalogram illustrated sleep as high-amplitude slow waves and wake as faster waves of low-amplitude. The stillness and immobilization of the body was assumed to be in correspondence with a decrease in brain activity. A milestone in the history of sleep disorders medicine and research was a more comprehensive depiction of brain-wave patterns in 1937 by Loomis et al. They also originated that sleep could be continuously measured along with the ability to recognize the presence of sleep and/or wake at any specified time without disrupting sleep. In 1949 Moruzzi and Magoun reasserted wake as a faster, more active state and sleep as a more synchronized, slower state by implanting electrodes into the brainstem reticular formation. They described wakefulness or EEG activation and sleep or EEG

synchronization as a continuum. In 1951, Starzl et al. used an animal model (cat) to show evidence that sensory collaterals discharged into the reticular formation, thus revealing a neural mechanism existed that transmitted sensory stimulation into lengthened activation of the brain and wakefulness. These results confirm evidence of a reticular activating system researched by Bremer in the 1930s.

In 1964, the fourth annual meeting of the Association of Psychophysiological Study of Sleep took place at Stanford University and began to take shape as a formal organization. Larry Monroe reported results from his research at the meeting in Los Angeles in 1967, and provided evidence that sleep scoring was highly unreliable. A great deal of the research during that time focused on the quantification of sleep stages as dependent variables in the investigation of human sleep. Homogeny of scoring sleep was imperative in order to move the research and clinical practices in a progressive direction. The development of the scoring manual required meticulous attention to detail as well as days of profound discussion to ensure its reliability. The product of this conference forms the basis for the scoring manual used in present day sleep research. At the time of development of the scoring manual sleep disorders medicine did not exist. The effort of all involved in the creation and standardization was the first agreement and venture in sleep disorders medicine.

The Associated Professional Sleep Societies define sleep disorders medicine as, "A clinical specialty which deals with the diagnosis and treatment of patients who complain about disturbed nocturnal sleep, excessive daytime sleepiness or some other sleep related problem." Unlike other medical specialties that deal with a primary organ system, sleep disorders medicine starts with a single organ; the sleeping brain and then

examines the impact of dysfunction of that organ on a wide array of other systems. Pathologies may primarily involve neuronal mechanisms or secondary effects on psychiatric, neurological, or medical conditions. The foremost identifiable characteristic of sleep disorders medicine is a full diagnostic evaluation of a sleeping patient. The broad scope of disorders spans a range from temporary jet lag to sudden unexplained death during sleep (Dement, 1990)

Basic mechanisms of sleep and wake

In 1917 Von Economo discovered a disease unrecognized up to that point in history, which he named encephalitis lethargica. While performing autopsies on his deceased patients, he discovered lesions concentrated within the posterior or anterior hypothalamus. His research revealed that while alive, patients with lesions localized with the posterior hypothalamus had problems staying awake while those with lesions in the anterior hypothalamus had problems staying asleep (or sleeping). These observations led to the first hypothesis that sleep was an active neural process rather than a passive process occurring after withdrawal of environmental stimulus (Lavie, 1993).

Jouvet proposed specific neurotransmitters contained within particular neuronal systems generate sleep and wake. Chemicals serving as neurotransmitters within the peripheral nervous system are present in the brain; drugs that act on these neurotransmitters have robust effects on wake and sleep. These neurotransmitters constitute molecules of different structure complexity and anatomical distribution, but communally, they partake in the constructing the human sleep-wake cycle.

What promotes wake?

The ascending reticular activating system is essential in maintaining cortical activation and behavioral arousal. The visceral, somatic, and special sensory systems provide collateral input to the neurons of the reticular formation as well as project by a dorsal pathway to the basal forebrain by way of the thalamus and ventral pathway. Pervasive impulses are relayed to the cerebral cortex from the thalamus and basal forebrain. Since the time of Economo, a dissociation of cortical activation and behavioral arousal of wakefulness have been found in humans and animals; two parallel systems controlled cortical activation and behavioral arousal have been discovered. Reduced cortical activation without a deficiency in behavioral response to stimuli was found in animals with lesions of the central midbrain tegmentum. The opposite was found in animals with lesions in the ventral tegmentum and hypothalamus; such an animal was behaviorally unresponsive and sustained cortical activation.

Activating system in the forebrain

The forebrain can independently generate cortical activation. Both thalamic and extrathalamic pathways transmit the activating stimulus of the reticular formation to the cerebral cortex. Research, in 1970, revealed neurons positioned within the posterior hypothalamus and basal forebrain that project to the cortical mantel initiate the relay to the cortex. The extrathalamic route and relay to the cortex is adequate for widespread cortical activation. Hypothalamic neurons were substantiated to be of great value in wake, given the destruction of nerve fibers of the posterior hypothalamus decreased wakefulness. The reticular formation provides ascending input to the posterior hypothalamus and the basal forebrain which subsequently project to the cerebral cortex.

In the continual dearth of input from the brainstem reticular formation, the systems of the forebrain act autonomously as activating systems and uphold cortical activation.

Neurochemicals of wake

Dopamine

Strong behavioral arousal can be generated by increasing the amount of dopamine in the synaptic cleft (through release). Increased concentrations of dopamine through inhibiting reuptake, or inactivation, or restraining enzymatic catabolism of dopamine also lengthen the duration of behavioral arousal. For that reason, wakefulness is decreased when the enzymes responsible for dopamine synthesis are inhibited. Cats experienced muscle rigidity and lacked behavioral response after dopamine-containing neurons in the substantia nigra and ventral tegmental area sustained a lesion. The dopaminergic neurons of these areas that project to the striatum and frontal cortex are an essential component of behavioral arousal. Akinesia and akinetic mutism cases often include ventral midbrain tegmentum or ventral posterior hypothalamus lesions in the location(s) of dopaminergic perikarya. Characteristics of parkinsonism include degeneration of dopaminergic neurons in the midbrain and dopamine depletion in the striatum. Dopamine release is greatest during wake, and it is highly associated with stimulating and lengthening behavioral arousal.

Norepinephrine

Norepinephrine produces prolonged vigilance associated with cortical activation. As with dopamine, increasing concentrations of norepinephrine through various mechanisms prolong arousal, and if synthesis is inhibited wakefulness is decreased.

Noradrenergic fibers ascend into the central midbrain tegmentum; in a cat, lesions in this area (of noradrenergic fibers) caused the cortical activation of wakefulness to severely decrease. Norepinephrine-containing neurons of the locus coeruleus and brainstem that project to the forebrain (and cortex) take part in an essential function of cortical activation. Normal enhancement and prolonged wakefulness of norepinephrine is demonstrated in that studies have shown cooling of the locus coeruleus produces sleep in a waking animal, and electrical stimulation produces arousal in a sleeping animal. During stressful, highly aroused, or attentive waking conditions, noradrenergic neurons of the locus coeruleus are the most active. During slow wave sleep, they gradually decrease rate of discharge until they nearly stop during REM sleep. Norepinephrine is important for initiating and sustaining activating processes in the thalamocortical systems.

Acetylcholine

Acetylcholine is an important neurotransmitter for waking. Impeding the breakdown of acetylcholinesterase enables acetylcholine to have extended postsynaptic action. This extended action prolongs cortical activation, thus improving vigilance. Nicotine and muscarine mimic the action of acetylcholine; they improve vigilance and cortical fast activity. Given the behavior of the cholinergic agonists, acetylcholine seems to take part in cortical activation (autonomously from waking behavior) during wake and REM sleep. Loss of vigilance and slowing cortical activity are effects of lesions of cholinergic neurons in the basal forebrain. Chemical agents that inhibit or inactivate cholinergic cells weaken the cortical activity and aroused states characteristic of wake and REM cortical activation. Increased release of acetylcholine from the thalamus during wake and REM sleep leads to cholinergic neurons of the pons and the mesencephalon

9

discharging at higher rates compared to slow wave sleep. Increased release of acetylcholine from the cortex during wake and paradoxical sleep also shows cholinergic neurons of the basal forebrain discharging at higher rates compared to slow wave sleep. Firing of pyramidal cells shifts to a tonic discharge associated with cortical fast activity as a result of excitation by acetylcholine. Cholinergic neurons of the brainstem and basal forebrain may influence transmission in the thalamus and the cortex by driving thalamocortical transmission and fast cortical activity during wakefulness and REM sleep.

Histamine

When administered directly onto cerebral ventricles, histamine has an arousing effect. Lesions of histamine-containing neurons in the tuberomammillary nuclei and posterior hypothalamus are associated with coma and decreased wakefulness. Posterior hypothalamus neurotoxic lesions result in slow wave and paradoxical sleep increases, as well as decreased wakefulness. Histaminergic neurons turn off during REM sleep and are most active during cortical activation in wakefulness. The tonic discharge in thalamic and cortical projections associated with waking activity is the result of histamine's action (excitatory, producing depolarization) on metabotropic receptors. During wakefulness, histamine promotes cortical activation.

Glutamate

Glutamate is the main excitatory neurotransmitter, and most likely the main neurotransmitter of the ascending reticular activating system. Some glutamate receptor antagonists act as sedatives; glutamate agonists produce seizures. Cortical activation of

10

spontaneous wakefulness or midbrain reticular formation stimulation causes the most release of glutamate form the cerebral cortex. In general, the postsynaptic receptors glutamate acts on are excitatory. Reticular formation neurons in the activating system, in the brainstem, and in the majority of the projection neurons in the forebrain, contain glutamate that is vital to a responsive waking state and cortical activation.

What promotes sleep?

Structures in the lower brainstem are capable of initiating the ascending reticular activating system of the upper brainstem which is suggestive of their importance in sleep generation. Research shows a transaction produced total insomnia when located in the brainstem behind the oral pontine tegmentum. Lesions of the lower pons or medulla reduced or abolished slow wave sleep. Research also shows the nucleus of the solitary tract and the neurons of the dorsal medullary reticular formation may perhaps spawn sleep. The 9th and 10th (glossopharyngeal and vagus) cranial nerve fibers relay afferent input from the thoracic and abdominal viscera receptors to the solitary tract. The solitary tract may have an effect on limbic forebrain structures and not work exclusively through inhibition of the reticular activating system.

Sleep generating systems in the forebrain

The thalamus was discovered to be the central hub for sleep in view of the fact that thalamic stimuli produced behavioral and EEG confirmed sleep. However, the thalamus is not obligatory for cortical slow wave sleep and behavioral sleep, as it is for cortical spindles. In addition to the brain stem, the anterior hypothalamus, basal forebrain and preoptic area are also central in sleep generation. Unaided, these structures are not

sufficient for slow wave sleep and must therefore be accompanied by involvement of the cerebral cortex and basal ganglia. The sleep generating system within the forebrain consists of neurons of the anterior hypothalamus, basal forebrain, preoptic area, and orbitofrontal cortex.

Neurochemicals of sleep

Serotonin

The blockade of serotonin break down augments and lengthens slow wave sleep. Accordingly, the inhibition of the enzyme in serotonin synthesis produces insomnia, reversible by immediate serotonin precursor administration. The location of the serotonergic neurons in nuclei of the brainstem indicates involvement in the slow wave sleep system of the brainstem. Partial lesions to the medullary, pontine, or midbrain raphe serotonin nuclei in a cat reveal the amount of sleep is proportional to the amount of serotonin left in the brain; a complete lesion generates insomnia. Given the results seen in the cat, serotonin raphe neurons appear to be fundamentally involved in the brainstem sleep generation system. With onset, and throughout slow wave sleep, serotonergic raphe neurons decreased firing and the release of serotonin during slow wave sleep decreased compared to wakefulness. Studies show serotonin is not involved in the maintenance of sleep, but instead they aid slow wave sleep onset. Results from the injection of serotonin into the basal forebrain showed decreases in cortical activity; this was suggestive of serotonin's constricting effect of cortical activation. During wake, serotonin could prime the brain for slow wave sleep by acting on many various types of cells and receptors, as well as encouraging sleep factors to build up.

Adenosine

In the brain and periphery, adenosine suppresses excitatory synaptic transmission; cholinergic neurons in the basal forebrain and brainstem can also be inhibited. Through multiple receptors it inhibits neuronal discharge and blocks nerve terminals from releasing neurotransmitter. The facilitation of burst discharge underlying slow wave sleep can occur through adenosine's hyperpolarizing action on projection neurons of the thalamus and cortex. Adenosine's action in the brain can be correlated with thalamocortical circuit mechanisms underlying slow wave sleep.

Gamma-aminobutyric acid (GABA)

GABA is crucial for initiating and maintaining sleep. By inhibiting post synaptic potentials, the neurons of the thalamic reticular nucleus inhibit and pace thalamocortical relay neurons. These neurons generating thalamocortical spindles contain GABA. The inhibition of the thalamus is critical for slow wave sleep and the subsequent loss of consciousness. Some GABAergic neurons project into the posterior hypothalamus where they can inhibit neurons of the activating system. In the posterior hypothalamus, the release of GABA in slow wave sleep is higher compared to wake and paradoxical sleep. In the cortex, release is also highly related to slow wave sleep. Particular GABAergic cells and/or receptors may be active during sleep, given GABAergic cells and receptors are active during wakefulness in all brain regions. Both types of receptors GABA acts on are generally inhibitory. In the thalamocortical system, both receptors are involved in decreasing membrane potential linked to spindling and slow waves. By initiating, pacing, and maintaining discharge mechanisms that underlie slow wave activity, and by

inhibiting activating systems, slow wave sleep onset and continuation in part depends on GABAergic transmission (Jones, 1994).

How do we measure sleep and sleepiness?

Analogous to hunger or thirst, sleepiness is a fundamental physiological need that contributes to the survival of humans. Sleepiness increases while awake and it includes functional impairment of concentration, drifting thoughts, blurred vision, heavy eye lids, sleep cravings, yawning, activity reduction, eye rubbing, head drooping and ptosis. Sleepiness is not able to be measured directly; it can only be described by the individual subjectively. The transition from complete wakefulness to evident sleep is largely depicted by the individual's report of sleepiness. The effects of sleepiness, such as sleep latency, cognitive impairments, and reaction time, can be measured directly and objectively. Objective assessments of these subjective complaints use sleepiness and vigilance tests in attempt to explain the source of the feelings. Vigilance involves wakefulness, alertness, and attention, for that reason, it is not considered simply an opposite of sleepiness. The multidimensionality of sleepiness and vigilance require an amalgamation of objective and subjective tests in order to obtain the most suitable description of the state or condition of the patient (Mathis & Hess, 2009).

Epworth Sleepiness Scale

The most widely used subjective questionnaire used in clinical practice is the Epworth Sleepiness Scale (ESS). This test is a self-administered and consists of eight questions. The test measures daytime sleepiness and assesses the likelihood of falling asleep while in eight different situations. The test taker rates the probability of falling

asleep in each situation on a scale of 0-3; out of a possible 24 points, a score of 5-6 is considered normal for a healthy adult (Johns, 1991). The straightforward questions and shortness of the test has greatly contributed to its high regard within the medical field. The ESS has also shown test-retest reliability, and it provides valid measures of sleep propensity in adults (Johns, 1991; Mathis & Hess, 2009).

Berlin Questionnaire

The Berlin Questionnaire is a product of the Conference on Sleep in Primary Care held in Berlin, Germany in 1996. Pulmonary and primary care physicians came to a consensus on the questions and content elicited by the questionnaire. The Berlin Questionnaire is subjective and assesses the presence of sleep disordered breathing by asking questions concerning risk factors and behaviors that have been proven to predict the presence of sleep disordered breathing. An introductory question and four subsequent questions relate to snoring behavior, three questions are directed towards daytime sleepiness and an ensuing question focuses on sleepiness while driving, and one question inquires about a history of high blood pressure. Body measurements and demographic information, such as ethnicity, age, sex, BMI, and neck circumference are also acquired in the questionnaire (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999).

Additional subjective tests

The Stanford Sleepiness Scale (SSS) is an additional subjective measure that assesses transient sleepiness (Mathis & Hess, 2009). The evaluation appraises symptoms and feelings using a self-rating Likert scale with seven degrees of severity (Johns, 1991). The inherent nature of the test allows for repeatability within a relatively short time

period. The visual analogue scale (VAS) and Karolinska Sleepiness Scale (KSS) also assess subjective sleepiness (Johns, 1991; Mathis & Hess, 2009).

Objective sleepiness scales

Self-reports of subjective sleepiness may not be dependable or consistent with the physical manifestations or presentation of sleepiness as observed by others. Patients usually underestimate and misjudge their own level of sleepiness, as only 72% of spouses agreed on the likelihood of falling asleep while watching television. Wrongful testimony may also be divulged to preserve a job or drivers license or to obtain prescription stimulant drugs. For this reason, objective measures also exist in attempt to gain a more complete understanding of the intricate complaint and problem of sleepiness (Thorpy, 1992).

Quantification measures of sleep continuity and quality

Polysomnography (PSG) is a medical diagnostic test intended to diagnose pathological conditions associated with sleep. The diagnostic test records and provides a considerable amount of activity within a range of organ systems over several hours. Sleep stage interpretation is achieved by obtaining concurrent documentation of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG) and respiratory recordings. The multiple recordings of the PSG illustrate all physiological events that occur during sleep and inform researchers or physicians about the individual subjects sleep architecture throughout the night. The EEG records electrical activity of the brain and reveals the amplitude and frequency of brain wave during sleep. The EOG records eye movements that are critical for scoring sleep

stages. The EMG measured the skeletal muscle activity, mainly of the chin. The ECG monitors the heart and detects arrhythmias and abnormalities. The simultaneous recording of the different physiological events and the novel metrics used to quantify sleep have been a large factor greatly contributing to the understanding and progression of sleep as an emerging scientific discipline (Minaritzoglou & Vagiakis, 2008).

PSG measurements of wake and sleep stages

Wake is characterized by alpha waves of 8-12 Hz with eyes closed and mixed frequencies together with beta waves of >13Hz with eyes open. The EMG shows high levels of activity, and the EOG shows voluntary eye movement, as if the person was looking around. Heartbeat and breathing are faster than in stage 1, 2, and slow wave sleep. Stage 1 has theta waves of 4-7.99 Hz (Figure 1 below).
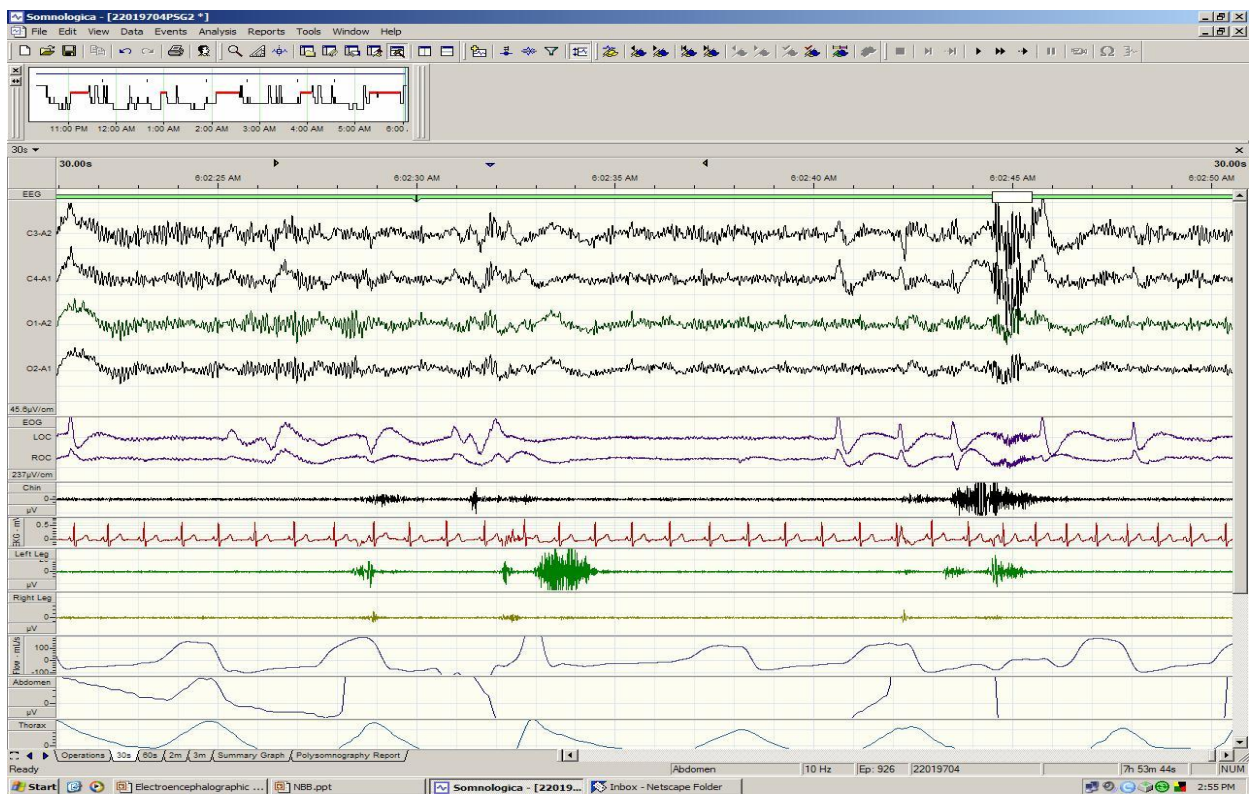
Figure 1

Stage 1 is characterized by a stable, tonic EMG, and patterns of slow rolling eye movement in the EOG. The ECG slows down slightly and becomes more regular, but there is no specific signal for stage 1. Breathing also slows down slightly from wake (Figure 2 below).
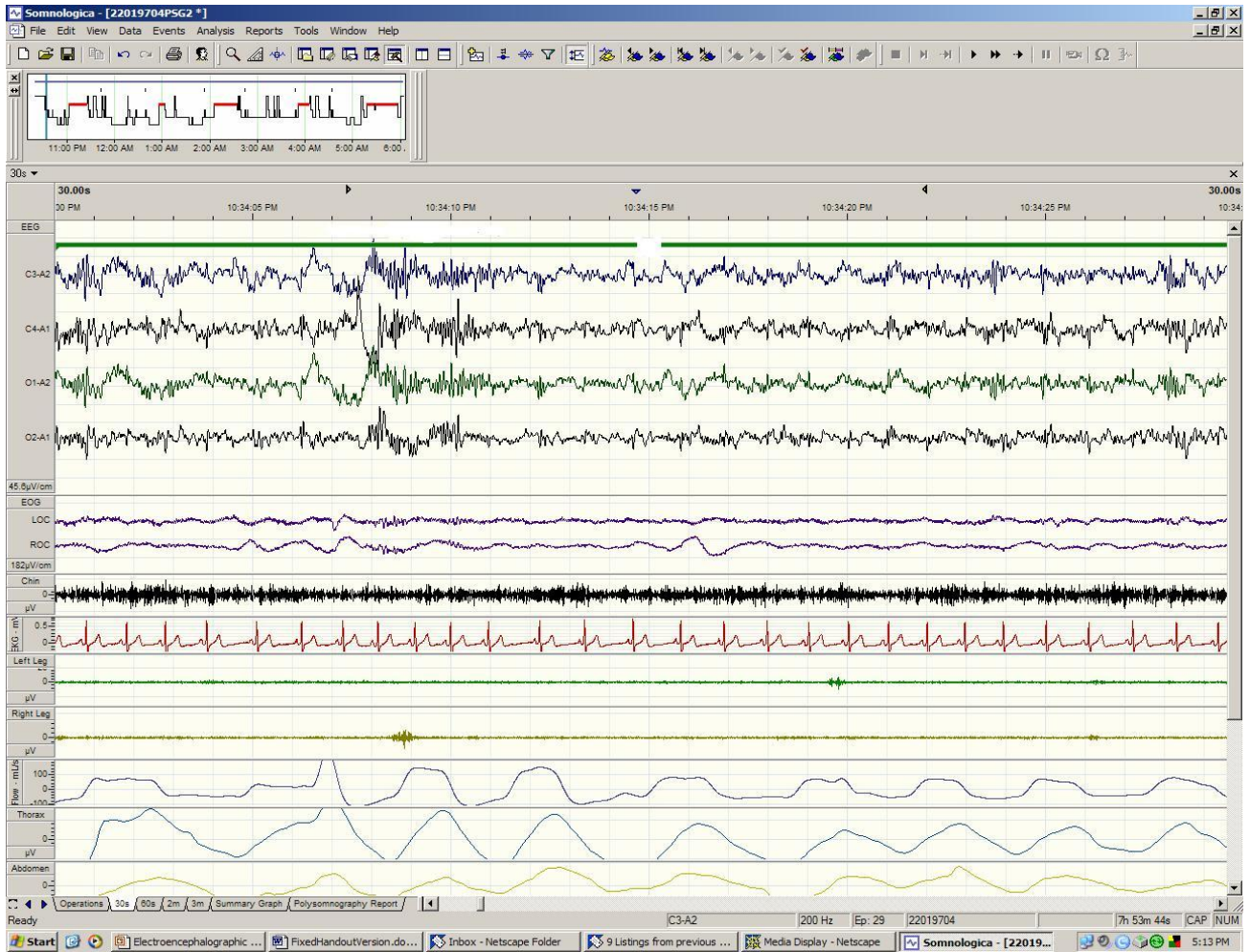
Figure 2.

Stage 2 is distinguished by theta waves (4-7.99 Hz), but the EEG must show spindles of

12-14Hz and k complex (sudden negative deflection followed by positive component) to

be considered stage 2. The EMG in shows a decrease in muscle tone compared to wake,

and the EOG shows little to no movement. Bodily functions slow down; the heartbeat and

breathing slow and becomes more regular (Figure 3 below).
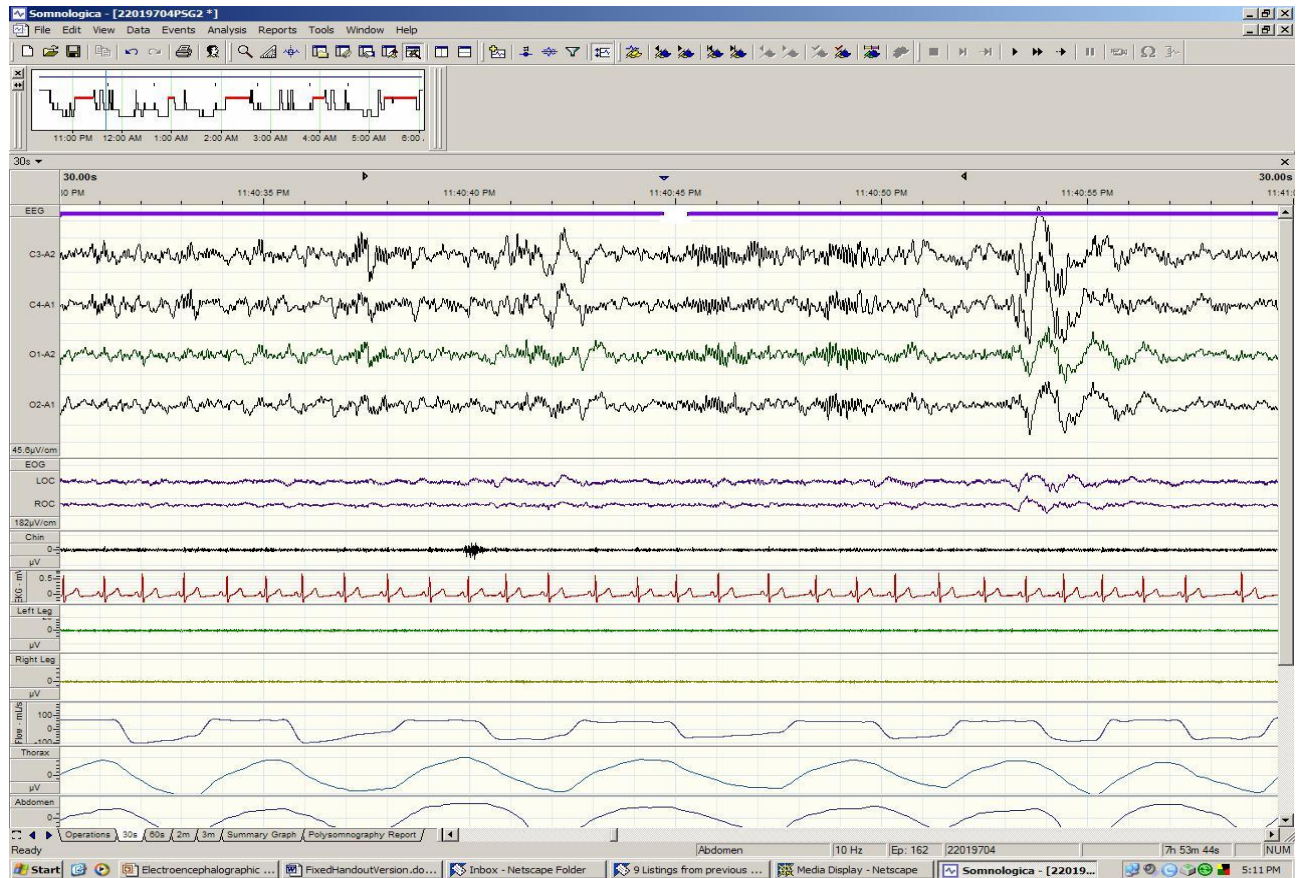
Figure 3.

Slow wave sleep (stage 3& 4) is characterized by delta waves of 0.5-4 Hz. The EOG may

show some activity, possibly resembling the activity of the EEG, and the EMG shows

little to no movement. The heartbeat and breathing are slow and regular in slow wave

sleep (Figure 4 below).
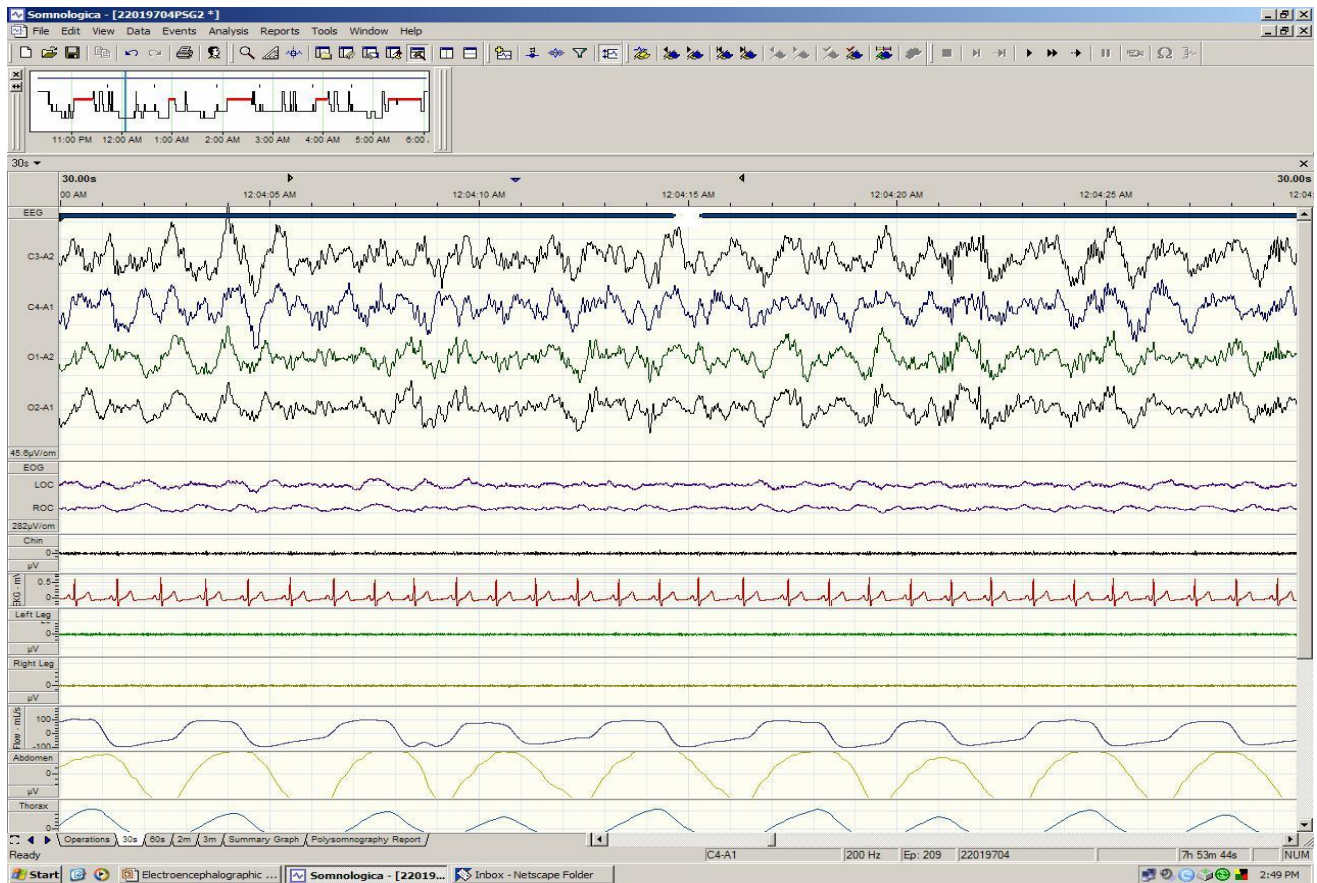
Figure 4.

REM sleep is illustrated by theta waves of 4-7.99 Hz. Low amplitude mixed frequency

waves often occur; alpha waves may occur at 1-2 Hz lower than in wake, and swatooth

waves of 2-6 Hz. REM sleep characteristics are shown by darting, quick movements of

the eyes out of phase as shown in the EOG, and muscle atonia shown in the EMG (bursts

of muscle activity may appear). The ECG shows an irregular heartbeat, and irregular

breathing occurs as well (Figure 5 below) (Minaritzoglou & Vagiakis, 2008).
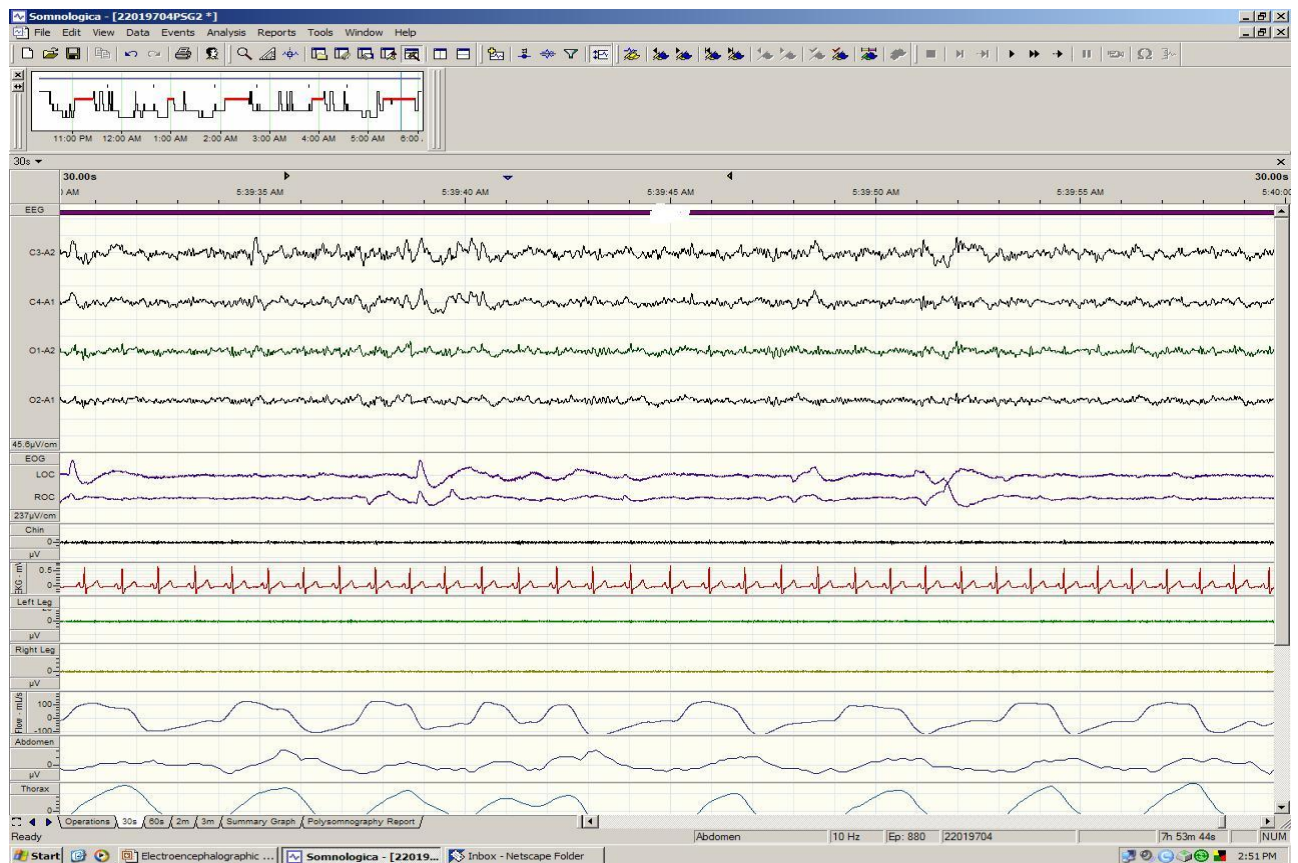
Figure 5.

Quantitative measure of daytime sleepiness

Daytime sleepiness is objectively measured using the Multiple Sleep Latency Test

(MSLT). The MSLT is used to establish differing degrees of sleepiness and/or to

ascertain a diagnosis of particular sleeping disorders. It is the most frequently used

objective diagnostic evaluation, and it stands as the only scientifically validated electrophysiological measure to assess the severity of excessive sleepiness. It computes the functional effects of sleepiness directly by measuring the readiness of a patient to fall asleep as well as sleepiness at two hour intervals during the normative wakefulness segment of the day (Thorpy, 1992).

The MSLT consists of four or five occasions in which sleep is suggested while the subject is in a dark, quiet room. Sleep onset, or latency, and specific sleep stages within sleep are measured by using standard electrophysiological methods (Carskadon et al., 1986) . Sleep latency is outlined as the time between "lights out" and the first epoch of (sleep any stage). In all naps, the average time from lights out until the first 30-second epoch scored as sleep is defined as the mean sleep latency. One or more epochs of REM sleep within 15 minutes from the first 30-second epoch scored as sleep is defined as sleep onset REM. A mean sleep latency of 10-20 minutes is considered normal, a latency of 5-10 minutes is considered borderline abnormal, and a mean sleep latency of <5 minutes is considered pathological sleepiness (Majer et al., 2007). Measuring and deciphering different sleep stages within the nap opportunities provides impertinent information relating to a diagnosis of narcolepsy or other disorders characterized by excessive somnolence (Carskadon & Dement, 1987).

Additional objective sleepiness measures

The Maintenance of Wakefulness Test (MWT) is a variation of the MSLT. It is administered under identical conditions as the MSLT, except the patient is in a semireclined chair and instructed to stay awake. It is commonly used to investigate an

improvement in alertness following a theraputic intervention (Thorpy, 1992). The Oxford Sleep Resistance Test (OSLER) and the psychomotor-vigilance test (PVT) are other tests used to quantify sleepiness by measuring reaction time (Mathis & Hess, 2009).

Both intrinsic and extrinsic factors can lead to varying levels of sleepiness. Narcolepsy, sleep apnea, RLS, and other sleep disorders are the main intrinsic etiologic factors associated with daytime sleepiness (Dauvilliers, 2006). Sleep deprivation (prolonging wakefulness) and sleep restriction (reducing sleep under the individual's baseline of usual required sleep) and the most common forms of extrinsic or behavioral factors leading to sleepiness (Reynolds & Banks, 2010). The MSLT has shown objective sensitivity in sleep disorders such as sleep apnea and narcolepsy and to the effects of sleep deprivation, sleep restriction, sleep fragmentation, and hypersomnia (Majer et al., 2007). These objective tests can identify daytime sleepiness as well as imply the presence of primary sleep disorders.

Chapter II

Literature Review

Sleep disorders

The International Classification of Sleep Disorders (ICSD) Diagnostic and Coding Manual was produced by the American Academy of Sleep Medicine in alliance with the European Sleep Research Society, the Japanese Society of Sleep Research, and the Latin American Sleep Society. The ICSD classifies more than 80 official sleep disorders (*International classification*, 2005). The impact, effects, presentation of symptoms, and impairments of each sleep disorder are extremely diverse and unique for each case. Several of the disorders are rather common, but the majority of the disorders have low prevalence within the population. In descending order, the most common disorders are insomnia, sleep apnea, restless legs syndrome, and narcolepsy (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008; "Sleep disorders," 2011).

Insomnia

Insomnia is the most common sleep disorder in the United States (Roth, Franklin, & Bramley, 2007). Insomnia symptoms are prevalent is 33-50% of the general adult population, and 10-15% are disturbed or impaired by the symptoms. Risk factors for insomnia include increased age, female sex, shift work, and concurrent medical, psychiatric, sleep and substance use disorders. Though not as common, low socioeconomic status and unemployment may also be considered risk factors. Research

suggests a positive relationship between insomnia and psychiatric disorders with an estimated prevalence (combined with chronic pain disorders) of 50-75% (Schutte-Rodin et al., 2008).

Insomnia is defined as the subjective experience of difficulty falling asleep, maintaining sleep, consolidation, or complaints of nonrestorative sleep disrupting daily functioning; these symptoms occur despite normative sleeping opportunities. Daytime impairments include trouble with attention, concentration or memory, poor performance in school and/ or social settings, mood disturbance, irritability, decreases in motivation and energy, increased probability of motor vehicle accident, and anxiety or distress over sleep. Physically, symptoms include fatigue, headaches, gastrointestinal problems and tension due to lack of sleep. A multi-parametric sleep studies and sleepiness quantification tests are not suggested in the customary diagnosis of insomnia, unless used to rule out other sleeping disorders. The Epworth Sleepiness Scale or another subjective sleepiness test is suggested along with a two week sleep diary and medical/psychiatric/medication questionnaire (Schutte-Rodin et al., 2008). A diagnosis of insomnia involves reported interference in daily life and anguish regarding the difficulties with nighttime sleep (Roth et al., 2007).

Insomnia can present as an isolated disorder; however, one or more comorbid medical or psychiatric conditions can exist in conjunction with insomnia. Patients suffering from chronic primary insomnia display signs of excessive anxiety and dwell in a state of hyperarousal. Physiologic changes that characterized hyperactivity are increased levels of catecholamines, increased basal metabolic rate, elevated body temperature, abnormal heart rate, increased level of central nervous system (CNS)

metabolic rate, and elevated EEG activity. The hyperarousal characteristic of insomnia had been hypothesized to be related to elevated activity of corticotropin-releasing factor (CRF) and overactive hypothalamic-pituitary-adrenal axis (HPA). The HPA is entailed in CRF discharge. CRF secretions act on receptors in the anterior pituitary causing the release of ACTH into the blood which then proceeds to instigate the productions and release of cortisol from the adrenal cortex. Insomnia patients have comparatively higher levels of adrenocorticotropic hormone (ACTH) and cortisol than do individuals without insomnia (Roth et al., 2007).

Sleep apnea

Sleep apnea is the second most common sleep disorder in the United States ("Sleep disorders," 2011). In the general U.S. population the prevalence of sleep apnea is estimate to be around 9% for women and 24% for men (Gottlieb et al., 2010). A diagnosis of obstructive sleep apnea (OSA) does not always come near the time of onset of the disease. Many patients and doctors alike have trouble identifying and detecting symptoms (Rahaghi & Basner, 1999). Given this, the average age of onset may be hard to detect. In children it is often referred to as growing pains, or misdiagnosed as ADHA. OSA can occur at any age, but prevalence and risk increases as age increases, given the high prevalence rates in those > 65 years of age (Levendowski et al., 2008; Bliwise, 2004).

The apnea hypopnea index (AHI) is most commonly used to determine OSA. A multi-parametric sleep study is scored for the number of apneas (cessation in airflow for at least 10 seconds) and hypopneas (a reduction in airflow of a certain magnitude for at

least 10 seconds associated with an arousal or desaturation). These test measurements can reveal the frequency and severity of desaturations related to the respiratory events. There are currently no valid or set standards to determine the severity of the disorder. A study assessing daytime sleepiness using a quantitative found the severity of hypoxemia as an independent predictor of a higher level of daytime sleepiness (short sleep latency) (Patil, Schneider, Schwartz, & Smith, 2007).

The night time symptoms of obstructive sleep apnea are frequent episodes of partial or complete upper airway obstruction hindering breathing. This results in repeated arousals and oxyhemoglobin desaturations during sleep. Other symptoms include insomnia and nocturia. Daytime symptoms typically include pathological hypersomnolence difficulties concentrating and sometimes depression (Patil et al., 2007). Central sleep apnea is a cessation in airflow during sleep without respiratory effort; in OSA there is respiratory effort during respiratory events. A great majority of the events in CSA are hypopneas. Despite the discrete definitions, CSA and OSA have many common characteristics involved in the basic mechanisms and clinical presentation (Malhotra & Owens, 2010). The typical patient presentation is a high BMI (obese), snoring, and witnessed apneas (strongest predictor of OSA). Signs of OSA include crowded pharyngeal airspace, abnormal positioning of the mandible, reduced circomental space, enlarges tongue, lateral peritonsillar narrowing, swelling in the lower extremities, tonsillar hyperplasia, and elevated mallampati score (Patil et al., 2007).

Increased fat deposits around the pharynx may have a compressive effect that has the potential to counteract the dilator muscles action of maintaining an open airway. A decrease in functional residual capacity of the lungs could lead to a decrease in tracheal

27

traction which in turn would increase pharyngeal collapsibility as well. Anatomical

mechanisms alone cannot account for collapses of the pharynx in OSA patients;

neuromuscular factors also play a role. A genioglossal EMG showed reduced activity at

apnea onset and increased activity with arousal when the airway reopened. A loss of

innervations of the upper airway muscles can lead to the collapse of the pharynx. It is

probable that a combination of both mechanical loads and impaired neuromuscular

response to the upper airway are needed to fully explain OSA (Patil et al., 2007).

RLS/PLMD

Restless leg syndrome is the third most common sleep disorder in the United

States ("Sleep disorders," 2011). Primary RLS begins in childhood or early adulthood

(symptoms develop slowly), and onset for secondary RLS typically occurs past age 45. It

is most commonly found in Northern Europeans and Northern Americans, with a

prevalence of 5-15%. Primary RLS is more common in women compared to men and

inceases with age (Bliwise et al., 2005; Ohayon & Roth, 2002; Stefansson et al., 2007).

Periodic limb movement disorder (PLMD) is estimated to be prevalent in about 3.9% of

the population. The prevalence is higher in women, as well as individuals 20-29 years of

age (Ohayon & Roth, 2002). Recent studies also estimate a higher prevalence of PLMD

in children with ADHD (Picchietti, England, Walters, Willis, & Verrico, 1998).

The symptoms (RLS) include an inherent need to move the legs (especially in

confined spaces such as in an airplane) as well as unpleasant sensations occurring in the

legs (or other body parts such as the arms, belly, jaw, etc) that come about more

frequently during the evening (Stefansson et al., 2007). Patients often complain about

burning, tugging, tightening, aching, and "a sensation of crawling insects inside the legs."

Excessive daytime sleepiness is associated RLS and PLMD due to the sleep disturbances

it causes (Littner et al., 2004).

Electromyography recordings from the anterior tibialis during a standard

nocturnal polysomnography are used to record periodic limb movements (Bliwise, He,

Ansari, & Rye, 2006). The nighttime symptoms (PLMD) are described as episodic and

cyclic typecast limb movement occurring in sleep. Due to the unpleasant sensations in the

legs/limbs, patients might report difficulty falling asleep or maintaining sleep. The

diagnostic criteria for RLS is the urge to move the legs accompanied by unpleasant

sensations in the legs, the worsening of these feeling during periods of rest, the relief of

these sensations by activity and/or movement, and worsening of the symptoms at night. A

measurement of four or more sequential muscle contractions that last .05-10 seconds

separated by 5-90 seconds that are 8 μV in amplitude is typically considered PLMD. All

other explanations for insomnia or hypersimnia must be ruled out as well for a diagnosis

of PLMD (Hornyak, Feige, Riemann, & Voderholzer, 2006; Walters & Rye, 2009).

RLS may be a result of dopamine dysfunction in the nigro-striatal brain areas. In

the striatum of RLS patients, advanced brain imaging has shown a decrease in dopamine

D2 receptor binding (Bliwise et al., 2005). Dopamine synthesis in the brain and the

regulation of dopamine receptors require iron. Unusually low Iron and ferritin have been

found in RLS patients, the striatum and red nucleus show reduced iron stores, and the

severity of RLS is inversely related to the amount of nigral iron (Ekbom & Ulfberg,

2009). Current studies have looked at the post synaptic change in neural response to

dopamine and dopamine levels outside the cell within the central nervous system. The

dopaminergic abnormality has yet to be explained; however, the latter of the two is fundamental to many hypotheses concerning neurochemical substrate underlying RLS symptoms (Allen, 2004). PLM may be related to insufficient dopamine levels as well, as it is more common in dopamine deficient conditions compared to conditions with dopamine excess (Littner et al., 2004). In clinical studies, PLMD has been associated with other mental and physical conditions such as diabetes, arthritic diseases, cardiovascular diseases, anemia, iron deficits, renal failure, obstructive sleep apnea, or affective disorders (Ohayon & Roth, 2002).

Narcolepsy

Narcolepsy is the fourth most common sleep disorder ("Sleep disorders," 2011). The archetypal age of onset is between the ages of 15-30; however, onset in younger children and older adults has been described. In the United States around 5% of patients seen in sleep clinics are diagnosed with narcolepsy (Littner et al., 2001). Stated by The National Institute of Neurological Disorders and Stroke (NINDS) within the National Institute of Health (NIH), narcolepsy is under-detected and under-diagnosed in the United States ("Sleep disorders," 2011).

It is characterized by irrepressible sleepiness and sporadic manifestations of REM sleep during normal waking times of the day (Littner et al., 2001). Other symptoms include cataplexy (sudden muscle weakness prompt by an emotional event), hypnagogic hallucinations (dreaming while awake), disjointed sleep, and an impermanent loss of muscle tone and lack of ability to execute voluntary movement at sleep onset or once awake (sleep paralysis). Thomas Kilduff headed a research team in the latter part of the

1990s that located a group of neurons in the hypothalamus, and labeled their new discovery hypocretin cells. Based on the anatomical and physical properties of the cells, they theorized the cells played a part in sleep and wake regulation. In 1999, two separate groups headed by Mignot and Yanagisawa discovered the pathophysiology of narcolepsy and neurochemical basis of the state of wake. They revealed a dysfunction or deficiency of hypocretin cells was correlated with the clinical symptoms of narcolepsy (Taheri, Zeitzer, & Mignot, 2002; Sutcliffe & De Lecea, 2002).

In patients thought to be narcoleptic, a nocturnal multi-parametric sleep study is preformed to establish any coexisting sleep disorders, and followed by testing to quantify the level of daytime sleepiness the next day. The MSLT is sensitive and reliable within the context of testing sleepiness due to narcolepsy; if other potential causes of excessive daytime sleepiness have been ruled out by a nocturnal PSG, the results of a MSLT can stand as diagnostic feature. A mean MSLT sleep latency of <5 minutes and two or more sleep onset REM periods (SOREMPs) is characteristic of 80% of narcoleptics. A clinical diagnosis of narcolepsy is contingent on the two main features of cataplexy or excessive daytime hypersomnolence. Cataplexy is difficult to detect and diagnose; unless cataplexy is observed by a clinician, the MSLT quantification of sleepiness is sufficient affirmation for the disorder (Thorpy, 1992).

Negative public health outcomes of sleepiness and lack of sleep

Sleep disorders affect more than one-third of the adult population. Sufficient sleep is interconnected with all aspects of life and healthy functioning (Bliwise, 2008). Daytime sleepiness has implications in public health far beyond its prevalence. It is

defined as the occurrence of sleepiness during a time when the individual would typically be expected to be awake and functional (Thorpy, 1992). Sleep restriction is a primary contributor to the development of daytime sleepiness (Punjabi, Bandeen-Roche, & Young, 2003). Medical conditions, sleep disorders, occupational demands, domestic responsibilities, and social/lifestyle choices also contribute to sleepiness and sizeable variance in sleep duration amongst the population and within individuals (Banks, Van Dongen, Maislin, & Dinges, 2010). Sleepiness has significant implications on quality of life by impacting occupational performance, driving ability, cognition, memory, and overall health (Carskadon & Dement 1987; Decker, Lin, Tabassum, & Reeves, 2008; Littner et al., 2001; Roth et al., 2007; Thorpy, 1992;).

Occupational effects

The occupational effects of daytime sleepiness have the potential to make many innocent people victims of catastrophic events. Performance tests administered after 17-19 hours of wakefulness show performance reductions equivalent to a blood alcohol concentration (BAC) of 0.05%. Tests administered around 20-25 hours of wakefulness show results similar to that of a BAC of 0.10% (Rajaratnam & Arendt, 2001). The melt down incident at the Three Mile Island plant in Pennsylvania was accredited to a human error of omission to correct a mechanical problem because of sleepiness (Mitler et al., 1988). In addition to Three Mile Island, Chernobyl, Bhopal, Exxon Valdez, and the Estonia Ferry disasters all occurred in the early morning hours and have been partially attributed to fatigue, sleepiness, and subsequent error. Sleepiness within the context of occupational effects has also been associated to loss of work hours, loss in productivity, and decreased earning and promotion capability (Thorpy, 1992). Research suggests

workers with sleeping problems were less satisfied with their job, scored lower

performance ratings, and missed more days (Kuppermann et al., 1995). Personnel in

essential workforce positions, such as health care workers, pilots, commercial drivers,

and nuclear power plant workers, are at an increased risk not only for their own safety,

but also for the safety of others as a result of fatigue and increased errors (Decker et al.,

2008; Thorpy, 1992).

Sleepiness and motor vehicle operation

According to U.S. statistics, 4% of deaths in motor vehicle crashes are due to

drowsiness, sleep, and/or fatigue. Self-reports of sleepy driving suggest a much greater

prevalence; drowsy while driving was reported at a prevalence of 29 to 55%, accounts of

falling asleep while driving were reported at 11-31%, and crashes due to sleepiness were

reported at a prevalence of 4-12%. Sleepiness causes more than 50,000 vehicle crashes

per year; second only to alcohol (Guilleminault & Brooks, 2001; MacLean, Davies, &

Thiele, 2003). A survey of long-haul, professional truck drivers discovered 40% had

difficulty staying vigilant on at least 20% of their drives, and another 20% reported

dozing off (Guilleminault & Brooks, 2001). Single-vehicle crashes are suspected to occur

due to driver lapses in attention. The distribution of crashed attributed to "falling asleep

at the wheel" illustrate two distinct peaks, with the most pronounced positioned between

midnight and 7am. Crashes from Israel, Texas, New York, Germany and the Netherlands

show similar, if not exact, temporal patterns (Mitler et al., 1988).

Cognition

Reduced sleep impairs cognition. Experimental restriction of sleep to five hours across seven nights showed immediate increases in subjective sleepiness and fatigue. Frequency of lapses in attention and psychomotor vigilance performance showed significant impairment after the second night of sleep restriction. The deficits in performance and mood variables showed cumulative growth in deficits across the entire study (Dinges et al., 1997). Sleep deprivation has toxic effects across nearly all areas of cognitive functioning. A meta-analysis shows simple attention and vigilance tasks were the two cognitive domains most affected by sleep deprivation, while complex attention and working memory were moderately affected. Speed and accuracy on simple attention tests were notably affected by one night of sleep restriction showing these deficits likely foreshadow further cognitive deficits and could function as admonitory signs for impending cognitive impairments (Lim & Dinges, 2010).

A combination of convergent and divergent skills are merged together to form the complex process of decision making. With a known probability of outcomes, healthy humans are typically risk seeking for loses but risk avoiding for gains. That is to say, if two options lead to a loss, the more risky option is chosen, but if two options lead to a gain, the less risky option is chosen. Deficient sleep causes individuals to be less risk avoiding for gain and less risk seeking for losses. The effect of lack of sleep on decision making greatly depends on how the outcomes are portrayed (a gain or a loss). Nonetheless, sleep deprivation diminishes sensitivity to risk, suggesting a higher inclination for perilous decisions (McKenna, Dickinson, Orff, & Drummond, 2007).

Memory

Sleep is important for the enhanced performing of learned tasks. Sleep is not a necessary factor for the learning and performance of tasks, but there is substantial evidence suggesting sleep can enhance performance (Siegel, 2001; Stickgold, 2005). Sleep contributes to the consolidation, and in particular, the augmentation of memories. The consolidation of memories does not depend on one particular aspect of sleep. Multiple sleep stages (REM, stage 2, and SWS) contribute to each type of memory consolidation differently. Different stages of sleep are proposed to have evolved to provide the most favorable brain states for the consolidation of different types of memory. While most processes related to sleep can also occur during wakefulness, experimental studies have suggested sleep dependent processing only occurs during sleep. When measuring sleep-dependent memory enhancement (tested by a visual texture discrimination test, a motor sequence test, and a motor adaptation test), study participants showed post-training improvement after sleeping for a night but not after a corresponding time awake. Results suggested the amount of time spent in certain sleep stages is associated with the amount of improvement during a night's sleep. The results also, suggest sleep deprivation can restrain overnight improvement and enhancement of performance, indicating these learning and memory processes only mature through sleep (Stickgold, 2005). In a separate study looking at behavioral alertness and sleep restriction, the subjects randomized the sleep duration of less than 7 hours showed remarkable steady deterioration in response time across the span of days. Sleep chronically restricted to less than 7 hours per night also showed notable daytime cognitive dysfunction such as state instability and reduced working memory (Banks & Dinges, 2007). Sleep an important function in acquiring and performing learned tasks.

Sleep is crucial for most favorable functioning in learning tasks, because interferences of sleep in wake will affect performance (Siegel, 2001).

Adverse health outcomes attributable to lack of sleep

Diabetes

Short sleep duration and incident diabetes are significantly associated. Short sleep time is also associated with hypertension and body weight, but when controlling for those variables, sleep has an independent effect on the incidence of diabetes. Insulin sensitivity and glucose tolerance are compromised in sleep deprivation. Increased sympathetic nervous system activation and decreased cerebral glucose consumption effect glucose tolerance. The brain utilizes nearly all non-insulin-dependent glucose; as a result of decreased uptake, higher concentrations circulate. Over time this higher concentration of glusoce could play a part in creating insulin intolerance. Also contributing to insulin resistance is the increased evening levels of cortisol resulting from sleep deprivation. Cortisol counteracts insulin inhibiting peripheral utilization of glucose; the increased load on the pancreas gradually compromises β-cell functioning and can lead to the development of type 2 diabetes. Research suggests individuals sleeping for five or less hours have a significantly higher risk for incident diabetes (Gangwisch et al., 2007; Mallon, Broman, & Hetta, 2005; Van Cauter, Splegel, Tasali, & Leproult, 2008).

Hypertension/Cardiovascular disease

Blood pressure and heart rate follow a daily pattern, or cycle, in which the lowest rates occur during sleep. Sleeping fewer hours per night increases the 24-hour blood pressure mean and heart rate, as well as exposes an individual to elevated level of activity

in the sympathetic nervous system for an extended amount of time. An increase in wake time exposes an individual to additional waking physical and psychosocial stressors; exposure to stressors, including sleep deprivation, raises blood pressure by increasing catecholamine synthesis. Structural adaptations, such as arterial and left ventricular hypertrophic remodeling, could occur as a result of shorter sleep duration and retune the cardiovascular system to operate at an elevated pressure equilibrium. As with diabetes, individuals sleeping less than 5 hours a night have an increased risk for incident hypertension (Gangwisch et al., 2006).

Obesity

Research suggests short sleep duration is a significant predictor of adult and childhood obesity. BMI is also significant in that for every additional hours of sleep, BMI was 0.35 kg/m2 lower. The majority of research suggests the association of BMI and sleep is stronger in younger populations, with one study finding the odds of obesity in children with shorter sleeping times 58% greater than those with longer sleeping times. Leptin and ghrelin are the two hormones necessitated in appetite regulation. Ghrelin is an appetite stimulant and leptin signals the brain the body has been fed, generating a feeling of satiety. Short sleep duration is associated with increased levels of ghrelin and decreased levels of leptin (Knutson, 2010). Sleep restriction is associated with increased hunger and appetite which in turn is correlated with a higher ghrelin to leptin ratio (Van Cauter et al., 2008). Total sleep time (recorded by a PSG) is inversely related to ghrelin levels, and leptin had been implicated as a probable intermediary in the association between adiposity and sleep duration. Longitudinal studies show individuals sleeping 5 or

fewer hours per night ultimately gain more weight (Knutson, 2010; Van Cauter et al., 2008).

Importance of study

The high prevalence of sleep disorders and the negative public health effects of daytime sleepiness demand attention. The objective quantification of daytime sleepiness and detection of sleep problems within a population based sample will provide epidemiologic prevalence data. This will not only expand on our current understanding of daytime sleepiness, but it will also raise awareness surrounding its significance and relation to public health.

Chapter III

Methods

The Institutional Review Board of the Center for Disease Control and Prevention (CDC) and collaborating institutions approved this study from which these data derive. The U.S. Department of Health and Human Services ethical principles and guidelines were followed in all procedures of the study to protect human subjects during research; participants were over 21 years old and were required to provide written confirmed consent.

Study population

The present data were generated from a study conducted from December 2002 to July in 2003 as part of the CDC program in fatigue surveillance (from 1997-2002). The surveillance study screened 56,146 adult residents, ages 18 to 69, currently living in Wichita by using a random digit-dialing telephone survey. The survey captured 5,295 individuals reporting fatigue lasting a period of time greater than or equal to one month. Of the identified persons with fatigue, 3,528 consented to participate in the surveillance study; 3,634 non-fatigued (NF) controls also participated in the study. Detailed phone interviews and clinical evaluations were conducted at 12, 24 and 36 month intervals, for the 7,162 participants. Based in the results of the surveillance study, 290 participants were invited to the clinical study; 227 consented to participate in the clinical study (Reeves et al., 2005).

In-hospital study

        Participants were admitted to a research unit in a Wichita hospital for two days. At the time of admission, all subjects were reevaluated for conditions that required exclusion from the study. During the two days in the Wichita research hospital participants provided urine and blood for standard analysis and went through a standardized medical history review and physical. The Diagnostic Interview Schedule for Axis I disorders was administered by explicitly trained and licensed psychiatric interviewers to detect the exclusion criteria of psychiatric conditions. The researchers used the Medical Outcomes Survey short form-36 (SF-36) (Ware & Sherbourne, 1992) to assess functional impairment, the Multidimensional Fatigue Inventory (MFI) (Smets, Garssen, Bonke, & De Haes, 1995) to determine fatigue severity (Decker, Tabassum, Lin, & Reeves, 2009).

Objective measures of nocturnal sleep and daytime sleepiness

        Sleep studies were conducted in Wichita, Kansas in a 4-bed clinical research unit of Wesley Medical Center. On the first night of the study the participants were asked to arrive three hours prior to their regular bedtime in order for the researchers to have sufficient time for electrode applications and bio-calibrations. On night #1 each participant underwent a standard nocturnal polysomnography. The following day the participants had a MSLT (administered and scored according to standard guidelines as described in Chapter II) to measure daytime sleepiness, followed by a second night of standard nocturnal polysomnography on night #2. The times of "lights out" and "lights on" were standardized for all subjects at 10:00 pm and 7:00 am. The MSLT began at

11:00 am the day after night #1, and consisted for three additional naps at 1:00 pm, 3:00 pm, and 5:00 pm.

Standard gold cup electrodes were utilized to record electroencephalography (EEG), electroencephalography (EOG), and electromyography (EMG) in the following arrangement: central EEGs (C3- A2//C4-A1), occipital EEGs (O1-A1//O2-A2) EEGs, left and right monopolar EOGs, surface mentalis EMGs, and a three lead electrocardiogram. These signals were collected at a sampling rate of 200 Hz. Inductance plethysmography-like belts around the chest and abdomen measured respiration, a pressure transducer with an attached nasal cannula measured airflow, a pulse oximeter probe was placed on the index finger to measure hemoglobin oxygen saturation, and EMG electrodes applied to the anterior tibialis muscles measured leg movement.

A registered polysomnology technologist scored all polysomnography data; the technologist was blinded to the classification each participant. Using the criteria for scoring sleep and respiratory variables based on the Sleep Heart Health Study, all data was manually scored as wake, stage 1, stage 2, slow wave sleep, or rapid eye movement (REM) sleep in 30 second epochs (Majer et al., 2007).

Study variables

Body mass index (BMI) was measured during the in-hospital physical, and age was obtained through self-report. Subjective levels of daytime sleepiness were also obtained through self-report by using a questionnaire-based survey, the Epworth Sleepiness Scale (ESS). Standard polysomnographic techniques were employed to obtain sleep efficiency (percentage of time asleep after lights out), total sleep time in hours (TST), and percentage of each sleep stage of total sleep (S1% of TST, S2% of TST, S3%

of TST, S4%of TST REM% of TST). The Respiratory Disturbance Index (RDI) is the total number of abnormal respiratory events divided by the total sleep time. The Limb movement Index (Lm Index) is the total number of limb movements, measured by PSG recording, divided by the total sleep time. The RDI and Lm Index were calculated prior to data entry. Mean sleep latency was obtained through the MSLT; it is calculated by averaging the time it took and individual to fall asleep in all 4 20-minute nap opportunities. A sleep onset REM period (SOREMP) (if it occurred) was detected through PSG measurements during the MSLT. The mean sleep latency and number of SOREMPs were also calculated prior to data entry. The recommendations for interpreting the MSLT made by Richardson et al. (1978) were used to recode the continuous variable (mean sleep latency) into a categorical variable with three levels: mean sleep latency of <5 minutes., mean sleep latency of 5-10 minutes., and mean sleep latency of >10 minutes.

Statistical analysis

PASW Statistics 18 was used for data management and statistical analysis purposes. Participants were separated into three groups based on MSLT mean sleep latency. Chi-square tests were used to examine differences for categorical variables. One-Way Analysis of Variance (ANOVA) was used to compare means for continuous descriptive variables. Bivariate and multivariate logistic regression analyses were used to test the association of each of the sleep variables with short and long sleep latency time, i.e. >10 minutes vs. <5 minutes. Logistic regression was also used to test the association of each of the sleep variables with ≥1 SOREM.

<center>**Chapter IV**</center>

<center>**Results**</center>

Sample Characteristics

The sample size for each variable used in the analysis is based on the consent of participants to provide specific data from the Wichita in-hospital study and clinical evaluation. Table 1 provides demographic information for the study sample (*n*=227). The majority of the sample were white females with a mean age of 50.2 (SD=9.0) and an average body mass index (BMI) of 28.7 (SD=4.8).

Table 1. Demographic Characteristics of Study Sample

Variable	N	(%)
Sex		
Female	186	81.9
Male	41	18.1
Race		
White	214	94.3
Black	8	3.5
Asian	1	.4
AM Indian/Alaskan native	1	.4
Multi	2	.9
	N	**Mean (SD)**
Age	227	50.2(9.0)
BMI	227	28.7(4.8)

The mean MSLT sleep latency of the four naps for the sample was 8.8 minutes (SD=4.9 minutes); 57 individuals (26.8%) had a sleep latency <5 minutes, 79 individuals (37.1%) had a sleep latency between 5-10 minutes, and 77 individuals (36.2%) had a

<center>43</center>

sleep latency > 10 minutes. Table 2 provides demographic information for these sleep latency groups. There were no significant differences between sex, BMI, or age between groups.

Table 2. Demographic Characteristics of Sample by MSLT Mean Sleep Latency

Variable	Mean sleep latency <5 min. (*n*=57)	Mean sleep latency 5-10 min. (*n*=79)	Mean sleep latency >10 min.(*n*=77)	*p* value
Sex (%)				.28
Male[a]	26.3(*n*=10)	47.4(*n*=18)	26.3(*n*=10)	
Female[b]	26.9(*n*=47)	34.9(*n*=61)	38.3 (*n*=67)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
BMI	29.2(4.6)	29.1(5.1)	28.3(4.7)	.53
Age	49.9 (9.1)	50.8 (7.8)	50.6 (9.6)	.82

a. (*n*=38)
b. (*n*=175)

Sleep quality and continuity

A mean MSLT sleep latency of 10-20 minutes is considered normal, a latency of 5-10 minutes is considered borderline abnormal, and a sleep latency of <5 minutes is considered pathological sleepiness (Majer et al., 2007). Table 3 shows results from ANOVAs comparing the three sleep latency groups on physiologic measures from the night prior to the MSLT and the Epworth Sleepiness Scale (ESS). Individuals with a sleep latency of < 5 minutes reported significantly higher levels of subjective daytime sleepiness on the self-administered ESS, than individuals with a sleep latency of > 10 minutes (*p*=.001). Sleep efficiency percent and total sleep time (TST) were also significantly different between the three groups. Individuals with a sleep latency of <5 minutes had significantly better sleep efficiency than those with a sleep latency of > 10

minutes (p=.001). Total sleep time of participants with a sleep latency of < 5 minutes and 5-10 minutes were significantly lower than participants with a latency of > 10 minutes (p<.0001). There were no significant differences between groups in sleep stage percentage of total sleep time (S1-4% of TST, REM % of TST), respiratory disturbance index (RDI), or limb movement index (Lm Index).

Table 3. Central Tendency of Sleep Architecture Data by MSLT Mean Sleep Latency

Variable	Sleep Latency <5 min. (n=57)	Sleep Latency 5-10 min. (n=79)	Sleep Latency >10 min. (n=77)	df	F	p value
	M (SD)	M (SD)	M (SD)			
ESS Score	11 (5)[a]	9 (5)[ab]	8 (5)[b]	(2,210)	6.72	.001
Sleep Efficiency %	90.0 (7.5)[a]	86.4 (8.4)[ab]	82.5 (14.8)[b]	(2,209)	7.88	.001
TST (minutes)	409.4 (44.3)[a]	385.8 (47.7)[a]	357.9 (77.4)[b]	(2,209)	12.50	<.0001
S1% of TST	8.3 (4.5)	8.3 (3.9)	8.9 (5.7)	(2,206)	.44	.645
S2% of TST	51.7 (9.2)	51.8 (9.9)	51.8 (9.6)	(2,206)	.001	.999
S3% of TST	11.9 (6.5)	11.1 (5.1)	12.8 (6.2)	(2,206)	1.42	.243
S4% of TST	5.9 (5.1)	5.5 (5.7)	5.9 (6.5)	(2,206)	.10	.907
REM% of TST	22.2 (6.5)	23.3 (6.7)	20.7 (7.1)	(2,206)	2.99	.053
RDI	5.7 (9.5)	5.0 (7.3)	5.8 (9.7)	(2,209)	.18	.109
Lm Index	9.8 (13.9)	6.7 (13.2)	5.2 (9.8)	(2,204)	2.24	.109

Means with different subscripts are significantly different based on Tukey's test at p < .05; ESS, Epworth Sleepiness Scale; TST, total sleep time; S1% TST, stage 1 percentage of total sleep time; S2% TST, stage 2 percentage of total sleep time; S3% TST, stage 3 percentage of total sleep time; S4% TST, stage 4 percentage of total sleep time, REM% of TST, REM percentage of total sleep time; RDI, respiratory disturbance index; Lm Index, limb movement index

Prevalence of sleep onset REM and previously unidentified sleep disorders

The presence of ≥1 SOREMP during the MSLT is suggestive of sleep restriction, sleep deprivation, or a sleep disorder, and is considered abnormal. As Table 4 illustrates, a total of 24 individuals had ≥1 SOREMP. A total of 46.9% (n=100) of the study sample

had unrecognized sleep disorders; 24.4% (n=52) had obstructive sleep apnea, 16.4%

(n=35) had periodic limb movements disorder (PLMD), and 2.3% (n=5) had narcolepsy.

The presence of ≥1 SOREMP was significantly different between the three sleep latency

groups (p<.0001). The presence of a sleep disorder was not significant.

Table 4. Prevalence of SOREMP and Primary Sleep Disorders by MSLT Mean Sleep

Latency

Variable	N	Sleep Latency <5 min. (*n=57*)	Sleep Latency 5-10 min. (*n=79*)	Sleep Latency >10 min. (*n=77*)	*p* value
# of Sleep Onset REM					
0	189	42	70	77	
1	18	10	8	0	
2	2	2	0	0	
3	4	3	1	0	
% with ≥1 SOREMP	24	26.3%	11.4%	0%	<.0001
Primary Sleep Disorders					
OSA	52	14	21	17	
PLMs	35	14	11	10	
Narcolepsy	5	4	1	0	
IH	2	2	0	0	
ISS	1	0	0	1	
Insomnia	1	0	0	1	
DSPS	2	0	0	2	
UARS	1	0	0	1	
CSA	1	0	1	0	
% with Primary Sleep Disorder	100 (%)	34 (59.6%)	34 (43%)	32 (41.6%)	.079

Note: OSA, obstructive sleep apnea; PLMs, periodic limb movements; IH, idiopathic
hypersomnia; ISS, insufficient sleep syndrome; DSPS, delayed sleep phase syndrome;
UARS, upper airway resistance syndrome; CSA, central sleep apnea

Predictors of mean sleep latency

The results of bivariate analysis of the association between each of the examined independent sleep variables and the mean sleep latency are shown in Table 5. The magnitude and direction of the association between the independent variables and the outcome are quantified using the odds ratio from the logistic regression models. The Epworth Sleepiness Scale, sleep efficiency percentage, total sleep time, and the presence of a sleep disorder were positively associated with a mean sleep latency of <5 minutes. Individuals with an ESS score of 11 or higher were significantly more likely to have a sleep latency of <5 minutes. Individuals with a sleep efficiency percentage of over 86%, TST of 6 or more hours, and the presence of a primary sleep disorder were also more likely to have a sleep latency of <5 minutes. RDI, specific sleep stage percentages of total sleep time, and Lm Index were not significantly associated with a mean sleep latency of <5 minutes.

Table 5. Associations of Sleep Related Variables to Mean Sleep Latency of <5 minutes

Variable	Threshold	Odds Ratio	95% CI	P value
ESS Score	<11 versus ≥11	3.162	(1.518-6.584)	**.0012**
Sleep Efficiency %	≤86% versus >86%	3.558	(1.631-7.758)	**.001**
TST (hours)	<6h versus ≥6h	5.064	(1.926-13.314)	**.001**
S1% of TST	1% increase	.977	(.912-1.046)	.499
S2% of TST	1% increase	.999	(.963-1.037)	.970
S3% of TST	1% increase	.979	(.926-1.035)	.448
S4% of TST	1% increase	.999	(.942-1.059)	.979
REM% of TST	1% increase	1.034	(.982-1.089)	.206
RDI	<5 versus ≥5	1.152	(.552-2.407)	.706
Lm Index	<5 versus ≥5	1.611	(.751-3.457)	.221
Has primary Sleep Disorder	No versus yes	2.079	(1.036-4.172)	**.040**

Multivariate logistic regression was used to determine the associations of each of the variables in the bivariate regression while controlling for the other covariates. Table 6

shows the results of the multivariate logistic regression; specific sleep stage percentages of total sleep time were excluded from the regression model due to multicollinearity with TST. The ESS was the only variable that remained significantly associated with a sleep latency of <5 minutes while adjusting for the other sleep variables. An EES score of 11 or higher was positively associated with a mean sleep latency of <5 minutes. Sleep efficiency percentage, TST, Lm Index, and the presence of a primary sleep disorder were no longer significantly associated with a sleep latency time of <5 minutes when adjusting for the other sleep variables.

Table 6. Multivariate Analysis Predicting a Mean Sleep Latency of <5 minutes

Variable	Threshold	Odds Ratio	95% CI	P value
ESS Score	<11 versus ≥11	3.450	(1.534-7.757)	**.003**
Sleep Efficiency	≤86% versus >86%	1.493	(.433-5.145)	.525
TST (hours)	<6h versus ≥6h	3.755	(.856-16.482)	.080
Lm Index	<5 versus ≥5	1.345	(.514-3.515)	.546
RDI	<5 versus ≥5	.593	(.207-1.702)	.331
Primary Sleep Disorder	No versus yes	2.122	(.790-5.701)	.136

Predictors of SOREMP

The results of bivariate analysis of the association between each of the examined independent sleep variables and the SOREMP are shown in Table 7. The magnitude and direction of the association between the independent variables and the outcome are quantified using the odds ratio from the logistic regression models. Sleep efficiency percentage, S4% of TST, and REM% of TST were positively associated with 1 or more SOREMP. Individuals with a sleep efficiency percentage of over 86% are more likely to have 1 or more SOREMP, compared to those with a sleep efficiency percentage of ≤ 86%. A 1% increase in S4% of TST increased the odds by 9% and a 1% increase in

REM% of TST increased the odds of 1 or more SOREMP by 7%. S1% of TST and S2% of TST showed a protective effect, or negative association with SOREMP. A 1% increase in S1% of TST decreased the odds of SOREMP by 16% and a 1% increase in S2% of TST decreased the odds by 6%.

Table 7. Associations of Sleep Related Variables to ≥1 SOREMP

Variable	Threshold	Odds Ratio	95% CI	P value
ESS Score	<11 versus ≥11	1.908	(.812-4.484)	.139
Sleep Efficiency %	≤86% versus >86%	5.299	(1.528-18.370)	**.009**
TST (hours)	<6h versus ≥6h	3.854	(.873-17.005)	.075
S1% of TST	1% increase	.841	(.728-.971)	**.018**
S2% of TST	1% increase	.938	(.893-.984)	**.009**
S3% of TST	1% increase	1.052	(.979-1.131)	.165
S4% of TST	1% increase	1.087	(1.015-1.164)	**.017**
REM% of TST	1% increase	1.075	(1.002-1.153)	**.043**
RDI	<5 versus ≥5	.878	(.346-2.231)	.785
Lm Index	<5 versus ≥5	.334	(.096-1.166)	.086
Has primary Sleep Disorder	No versus yes	1.386	(.591-3.249)	.453

Multivariate logistic regression was used to determine the associations of each of the variables in the bivariate regression with the outcome variable of 1 or more SOREMP while controlling for the other covariates. Table 8 shows the results of the multivariate logistic regression. None of the variables significantly associated with 1 or more SOREMP in the bivariate analysis remained significant when adjusting for the other sleep related variables. The presence of a primary sleep disorder became significant while controlling for other covariates; individuals with a sleep disorder were more likely to have 1 or more SOREMP compared those without a primary sleep disorder. Lm Index also became significant; however, it was negatively associated with the outcome variable. A Lm Index of ≥5 showed a protective effect by decreasing the odds of 1 or more SOREMP by 81% when adjusting for the other sleep variables.

Table 8. Multivariate Analysis Predicting ≥1 SOREMP

Variable	Threshold	Odds Ratio	95% CI	P value
ESS Score	<11 versus ≥11	1.745	(.706-4.313)	.227
Sleep Efficiency	≤86% versus >86%	5.027	(.722-34.997)	.103
TST (hours)	<6h versus ≥6h	.950	(.094-9.554)	.965
Lm Index	<5 versus ≥5	.190	(.046-.786)	**.022**
RDI	<5 versus ≥5	.473	(.120-1.596)	.210
Primary Sleep Disorder	No versus yes	3.478	(1.023-11.821)	**.046**

Chapter V

Discussion

In our society sleep is often the first and most dispensable commodity. There are many costs associated with sleep deprivation and sleep restriction. Although these are not the sole factors contributing to daytime sleepiness, they do appear to account for a great portion of it (Ohayon, 2008). The prevalence of excessive daytime sleepiness is estimated to be between 12-15% within the general population. The pervasiveness of daytime sleepiness notably contribute to the public health burden of motor vehicle crashes, decreased occupational performance, cardiovascular events, cognition and memory impairments, and all-cause mortality. Predisposing factors include voluntary sleep restriction, sleep deprivation, and sleep fragmentation due to sleep disorders (Lim & Dinges 2010; Punjabi et al., 2003; Siegel, 2001; Stickgold, 2005).

Daytime sleepiness is typically defined as the occurrence of sleepiness during a time when the individual would typically be expected to be awake and functional (Thorpy, 1992). Sleepiness is a complaint, thus it is only able to be subjectively described by the individual (Mathis & Hess, 2009). Sleepiness is complex and the difficulty in defining and measuring certain features is well known (Bliwise, 2001; Kim & Young, 2005). A standardized operational definition of daytime sleepiness is nonexistent, and very few subjective surveys have used parallel definitions (Ohayon, 2008). The effects of sleepiness, such as sleep latency, cognitive impairments, and reaction time, can be measured directly and objectively. Objective assessments of these subjective complaints

use sleepiness and vigilance tests in attempt to explain the source of the feelings (Mathis & Hess, 2009). Various studies have been conducted investigating the relationship between subjective and objective measures; the findings are inconsistent, ranging from minimal to moderate associations (Benbadis, et al., 1999; Chervin & Aldrich, 1999; Chervin, Aldrich, & Pickett, 1997; Johns, 1991; Johns, 1994; Punjabi, et al., 2003; Sangal, Mitler, & Sangal, 1999).

Previous research quantifying daytime sleepiness has been conducted using subjective measures or conducted within a clinical population; there is a lack of large-scale, normative data on daytime sleepiness in samples representative of the general population. The purpose of this study was to provide population based data using physiologic and objective measurements to quantify the objective level of daytime sleepiness. This will not only provide valid and reliable results for the distribution and prevalence of the level of daytime sleepiness, but also raise awareness surrounding the impending negative public health effects.

Summary of primary findings

The sample for this study included 227 participants, with the majority of the sample being white females around 50 years of age. Participants were screened in a detailed phone interview and reexamined in a clinical evaluation to detect for any medical or psychiatric conditions. A current sleep disorder, a prior sleep disorder diagnosis, or sleep complaint were also considered exclusionary conditions. Each participant underwent standard nocturnal polysomnography and a standard multiple sleep latency test (MSLT) on the subsequent day.

The mean (SD) sleep latency of the sample was 8.8 (4.9) minutes; 26.8% had a mean sleep latency <5 minutes, 37.1% had a mean sleep latency between 5-10 minutes, and 36.2% had a sleep latency > 10 minutes. Twenty-four individuals had ≥1 SOREMP and were significantly sleepier than individuals without SOREMP. A total of 100 individuals had a previously unidentified sleep disorder. The most common sleep disorders were sleep apnea (24.4%), periodic limb movements in sleep (16.4%), and narcolepsy (2.3%).

Individuals with shorter sleep latencies, compared to those with longer latencies reported higher levels of subjective sleepiness, had better sleep efficiency percentages, and longer sleep times. The Epworth Sleepiness Scale, sleep efficiency percentage, total sleep time, and the presence of a sleep disorder were positively associated with a mean sleep latency of <5 minutes. Sleep efficiency percentage, S4% of TST, and REM% of TST were positively associated with ≥1 SOREMP; S1% of TST and S2% of TST were negatively associated with ≥1 SOREMP

SOREMP

The prevalence of SOREMPs in this study sample are comparable with the findings of another recent study conducted by Singh, Drake, and Roth (2006), assessing the prevalence of SOREMPs in a population-based sample. The population-based study conducted in southeastern Michigan studied 333 participants and found ≥2 SOREMP at a prevalence of 3.9%. In the current study sample, 2.8% had ≥2 SOREMP. The percentage of individuals with 0, 1, 2, and 3 SOREMPs in the Singh et al. study are distributed as follows: 86.7%, 9.4%, 2.5%, and 1.1% (two individuals with >3 SOREMPs). In the

current study, the distribution of 0, 1, 2, and 3 SOREMPs are as follows: 88.7%, 8.5%, 0.9%, and 1.9%. The two studies are also similar in that an inverse relationship was found between SOREMP and mean sleep latencies; a higher prevalence of SOREMPs were found in the individuals with shorter mean sleep latencies. Singh et al. (2006) found the only sleep-related variable significantly associated with SOREMPs was excessive daytime sleepiness (low mean sleep latency), objectively measured by the MSLT. Our study also found a significant relationship between SOREMP and sleep latency time.

The occurrence of SOREMP was described by Vogel in 1960 and later associated with narcolepsy by Rechtschaffen et al in 1963 (Rechtschaffen & Wolpert, 1963; Vogel, 1960;). REM onset was found to be exclusively associated with narcolepsy in the 1960's, and the first definition of this disorder included irregularities of REM (Oswald, 1976). Subsequent studies confirmed that the appearance of ≥2 SOREMPs were considered pathognomonic to narcolepsy and considered "highly diagnostic." These studies were challenged in the 1980s by findings of SOREMPs in patients with periodic limb movements, sleep apnea, and healthy young adults. (Mignot et al., 2006; Singh et al., 2006). Causes of SOREMPs have been identified, including REM sleep deprivation, alcoholism, drug withdrawal, major depression, and sleep-wake schedule abnormalities, and must be controlled for in studies examining factors contributing to SOREMP (Singh et al., 2006).

Very few studies have been conducted outside of a clinical population to assess the prevalence of SOREMP in healthy controls. The high prevalence of SOREMP found in our population-based sample corresponds with other findings from studies in a healthy sample. A study conducted in 1998 by Geisler et al., found ≥1 SOREMP in 11% (n=100)

of a healthy sample, and ≥2 SOREMP in 3% of the sample. The prevalence of ≥1

SOREMP in our study was 10.9%, and the prevalence of ≥2 SOREMP was 2.7%. An

additional study conducted in by Mignot et al. (2006), also found a high frequency of

SOREMP during the MSLT in a random sample of healthy adults. Consistant with our

study, multiple studies have found subjective sleepiness and total sleep time are not

significantly associated with SOREMP, and a significant association with sleep latency

time (Bishop, Rosenthal, Helmus, Roehrs, & Roth, 1996; Mignot et al., 2006; Singh et

al., 2006). Collectively with our study, initial studies conducted within healthy samples

suggest SOREMPs are not only present in sleeping disorders and point towards an

alleged higher prevalence in the general population (Mignot et al., 2006).

Sleep disorders

The presence of a significant percentage of sleep disorders within our study

sample validate prior suggestions that such disorders remain unrecognized, undiagnosed,

and untreated (Roth, 1995; "Wake up America," 1993). Lack of health care provider

education of sleep disorders is stated as one reason for this deficit. In a four-year medical

school program curriculum in the United States, an average of 2 hours of content is

provided in sleep medicine. Didactic teaching (of more than 4 hours) on sleep is offered

in less than 5% of medical schools, and of this 5%, most are offered as elective courses in

the 4th year. A mere 8% of medical students are trained in sleep lab procedures, and only

11% have take part in the clinical evaluation of patients with sleep disorders. This

suggests the level of knowledge and education within the health care field is lacking,

despite the substantiation of sleep as an intricate part of healthiness and wellbeing

(Rosen, Rosekind, Rosevear, Cole, & Dement, 1993).

Obstructive Sleep Apnea

The most prevalent sleep disorder detected through the nocturnal PSG in this study was obstructive sleep apnea (OSA). OSA was detected in 28.2% of males and 23.7% of females (24.9% of the total sample). The detected prevalence of OSA in females of this study was much higher than estimates of 9% in the general U.S. population, but the detected prevalence of OSA in males of this study was comparable to estimates of 24% in the general U.S. population (Gottlieb et al., 2010).

Health care providers often fail to recognize, or see importance in, major risk factors and symptoms associated with OSA (Rahaghi & Basner, 1999). It is estimated that 93% of women and 82% of men with moderate to severe sleep apnea may go undiagnosed (Young, Evans, Finn, & Palta, 1997). Obstructive sleep apnea is just beginning to gain recognition as one of the most under-diagnosed chronic diseases. The resultant morbidity and mortality from OSA exceed that of any other sleep disorder. Negative health outcomes include daytime sleepiness, as well as coronary artery disease, hypertension, myocardial infarction, cardiac arrhythmias, diabetes, and increased risk of congestive heart failure (Levendowski et al., 2008).

Periodic Limb Movements in sleep

The second most detected sleep disorder was periodic limb movements in sleep (PLMS). The detected prevalence of PLMS within our study sample was 16.4%. PLMS is detected in standard nocturnal sleep studies at a prevalence rate of 25% in patients without RLS, but are typically read as incidental findings associated with alternate sleep disorders. PLMS is present in 90% of patients with restless legs syndrome (RLS) (Trotti

et al., 2009; Walters & Rye, 2009). PLMS occurring in individuals with insomnia and/or hypersomnia that is not explained by another factor is considered PLMD. The largest epidemiological study conducted to date assessing PLMD and sleep complaints, found a prevalence of 3.9% in a study sample of 18,980 participants (Ohayon & Roth, 2002).

PLMS can result in fragmented sleep, insomnia, and excessive daytime sleepiness. In turn, daily functioning and quality of life are impacted as well (Ohayon & Roth, 2002). PLMS is associated with a physiologic arousal response measured by the electroencephalographic (EEG), called a microarousal. Heart rate changes have also been observed in 99% of individuals with PLMS, and consistently occur prior to the movement. This suggests the autonomic activation is not a cardiac response to motor activation, but instead takes part in the arousal process (Gosselin et al., 2003). Multiple studies have shown significant relationships between PLMS and hypertension, cardiovascular disease, and cerebrovascular disease; however, a direction of causality has not yet been established (Trotti et al., 2009; Walters & Rye, 2009).

Narcolepsy

The third most detected sleep disorder detected in this study was narcolepsy, prevalent in 2.3% of our study sample. This prevalence is much higher than the population-based estimates of .02-.07% (Hublin, Partinen, Kaprio, Koskenvuo, & Guilleminault, 1994; Longstreth, Koepsell, Ton, Hendrickson, & Van Belle, 2007).

As with sleep apnea, narcolepsy is also under-recognized and under-diagnosed. The disorder has a variety of symptoms and subtle onset, but the public as well as health professionals are unfamiliar with the disorder. Major symptoms of narcolepsy are not

exclusive to the disease, thus many patients are unaware they are facing the onset of a marked neurological disorder and do not seek medical advice. The considerations of symptoms alone can cause great difficulty in establishing an accurate diagnosis of the disorder due to the lack of specificity (*Narcolepsy Fact Sheet*, 2010). Without early detection and treatment, narcolepsy can significantly impact quality of life. A major effect of narcolepsy is excessive daytime sleepiness; driving impairments are also very prevalent, along with negative occupational effects and increased risk for crashes and injury (Broughton et al., 1981). Narcolepsy can also impair education, the establishment of relationships, family life, and social activities (Daniels, King, Smith, & Shneerson, 2001).

Insomnia

Insomnia is the most common sleep disorder in the United States with symptoms prevalent is 33-50% of the general adult population (Roth et al., 2007; Schutte-Rodin et al., 2008). Insomnia is defined as the subjective notion of difficulty falling asleep, maintaining sleep, consolidation, or complaints of nonrestorative sleep disrupting daily functioning (Schutte-Rodin et al., 2008). The focus of this study was the quantification of daytime sleepiness through use of objective measures. The appropriate subjective measures for detecting insomnia were not employed in the current study, thus the numbers obtained from the study are not representative of the actual prevalence rate of the disorder.

Epworth Sleepiness Scale

The significant association of the ESS with the mean sleep latency as measured by the MSLT in this study is comparable to previously published studies. A study examining data from the Wisconsin Sleep Cohort Study (a representative sample from the general population) determined scores on the ESS were associated with MSLT mean sleep latency. A moderate association was found; individuals with an ESS scores of 6-11 were at a 30% increased risk for sleep onset and individuals with an ESS score >12 were at a 69% increased risk for sleep onset during the MSLT. Multiple other comparisons of results from the ESS and MSLT have found similar findings (Johns, 1994; Johns, 1991; Punjabi et al., 2003).

The data presented here diverge from a number of previous reports that have found weak or no significant association between the ESS and the MSLT (Benbadis et al., 1999; Chervin, et al., 1997; Chervin & Aldrich, 1999, Sangal et al., 1999). Reasons for inconsistency among studies could be due to the differences in study populations and sample size (Sangal et al., 1999). The controversial nature of this finding suggest that future research is needed within representative population-based samples to determine the associations between self-report measures of sleepiness and objective measures of daytime sleepiness.

Limitations

Limitations of this study reflect aspects of the study design. The participants of the study represented a population-based sample. However, the population was oversampled for fatigue; therefore, the number of fatigued individuals in the sample must be considered. In general, participants were overweight or obese. Obesity has been

59

distinguished to have an effect on sleep, thus the results cannot be generalized to individuals with a normal BMI (Knutson, 2010; Van Cauter et al., 2008). In addition, the majority of the study sample was older women. Menopausal status has a notable impact on sleep, and this report did not include data pertaining to menopausal status (Young, Finn, Austin, & Peterson, 2003). We also did not have data on whether our participants were working night or rotating shifts. Night shift workers are at higher risk for sleepiness than day shift workers (Akerstedt, 1988; Akerstedt, 1995; Akerstedt, 2003). As with other limitations above, further studies must be conducted to explore these differences in order to expand our understanding of daytime sleepiness.

Future directions

The cross-sectional design of this study does not allow for the establishment of causality. The substantial public health burden of daytime sleepiness requires consideration; however, much of the current data has come from measures within a clinical population or by using subjective assessments (Breslau, Roth, Rosenthal, & Andreski, 1997; Punjabi, et al., 2003). Epidemiologic data substantiating objective levels of daytime sleepiness within the general population are insufficient and further studies with a larger, more representative sample size is necessary. Population-based studies using objective measures are essential in provide prevalence data and risk factors associated with daytime sleepiness, as this information is important for the future of sleep disorders research. The imminent role for of public health within this area of research is not only in the future research, but also in education, the promotion of healthy sleep habits, and prevention.

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