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PRIMARY CARE EDITION

EDITOR-IN-CHIEF
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Dear Colleagues,

Welcome to this first issue of *The International Journal of Sleep and Wakefulness – Primary Care.*

Sleep is an active state, critical for our physical, mental, and emotional well-being. Sleep is also vital for optimal cognitive performance, with disruption resulting in functional impairment. At any given time, it is estimated that 50% of adults in the US are affected by a sleep disorder such as difficulty in falling or staying asleep, in staying awake, or in adhering to a consistent sleep/wake schedule.

The International Journal of Sleep and Wakefulness – Primary Care, and its sister publication *The International Journal of Sleep and Wakefulness*, are two new CME-accredited journals that have been developed to identify and highlight the important advances in this area. These quarterly journals will provide access to a critical and clinically relevant review of information regarding disorders of sleep and wake. Each issue will include major review articles authored by leading specialists. These manuscripts are peer-reviewed for quality and CME accredited to provide an ongoing educational resource. In addition, summaries and analyses of recent papers, chosen for their impact upon the field, are provided for the reader together with highlights from recent international conferences.

In the "Foundations in Sleep" section, Drs Lieberman and Neubauer give an overview of the physiology and regulation of normal sleep and wakefulness. They describe how this changes with age and also briefly review some of the more common sleep disorders likely to be encountered by primary care physicians.

In the first leading article, Drs Mallis, Brandt, and Rosekind discuss the impact modern around-the-clock work schedules upon society. Disruption of the normal sleep/wake cycle can lead to sleep loss, degraded performance and mood, and increased risks to safety and health. Shift-work sleep disorder is estimated to affect 10% of those working non-standard schedules, the authors highlight the need for a comprehensive approach to address the risks to health and safety associated with shift work.

Short sleep duration is one of the many factors purported to contribute to the obesity problem we are currently facing. Data have indicated that shorter sleep can cause alterations in the circulating levels of certain metabolic hormones, leading to changes in appetite, body weight and composition, and energy expenditure. A number of possible mechanisms are proposed for the interaction between sleep and metabolism and, as Dr Taheri suggests, there can be little risk in including adequate sleep amongst the advice for healthy lifestyle approaches to help combat the obesity epidemic.

Finally, in our "In Focus" section, Professor Zee and Ms Wolfe provide insight into the workings of a clinical sleep laboratory, so as to better equip the primary healthcare provider when informing and reassuring patients being referred to such clinics.

These articles are followed by a clinical review section containing concise and critical analyses of recently published papers from the latest international literature in the field of sleep and wake disorders, examining research findings, and explaining the clinical importance of the results.

This issue concludes with meeting reports detailing the most important presentations relating to disorders of sleep and wake from Sleep Medicine 2007 and the 25th Annual Annenberg Conference of Sleep Disorders in Infancy and Childhood.

We hope you find *The International Journal of Sleep and Wakefulness – Primary Care* an informative and interesting publication. On behalf of the Editorial Board and the Publishers, I would like to welcome you to this first issue and look forward to receiving your comments on the material presented or suggestions for future topics to help us ensure the content is as comprehensive as possible.

Alan F Schatzberg
Editor-in-Chief

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Normal Sleep and Wakefulness

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Our understanding of sleep and wakefulness has increased significantly in the last half century. Prior to the 1950s, sleep was thought to occur as a result of fatigue, and it was assumed to be associated with reduced brain activity. Over the years, and following vigorous investigation of the topic, our knowledge of sleep has both dramatically expanded and significantly changed. We now know that sleep is an active process involving every organ of the body, and is highly regulated by the central nervous system. In fact, during sleep, individuals exhibit unique and sometimes very active brain processes, comparable to when awake. Sleep is a dynamic, not a static state.

Although we do not know precisely why we need sleep, or how it may be beneficial, multiple observations and associations suggest that sleep serves numerous important functions. For example, experimental studies have shown that laboratory animals deprived of sleep actually die sooner than those who are allowed sleep but are deprived of food [1]. We also know that there is a tremendous drive to sleep. Adults spend about a third of their time sleeping; neonates spend approximately double that amount of time. Additionally, we find that most people have great difficulty in going for longer than 24 h without sleep, and sleep deprivation in humans rapidly leads to cognitive and psychomotor impairment. These, as well as other examples, support the notion that sleep is important for the overall health and survival of an individual, but the definitive answer as to why we need sleep, and exactly how it benefits us, is yet to be fully elucidated [2,3].

We do know that sleep is a reversible behavioral state (differentiating it from coma, which is also reversible but usually with greater difficulty) during which a person is perceptually disengaged from his or her environment. However, this disengagement is not absolute. For example, mothers frequently can hear their infants whimper and be awakened from sleep, while not hearing nor responding to other, louder, sounds that hold less meaning for them. It has been observed that individuals can become attuned to a certain sound or sounds that will awaken them from sleep, while other noises go unnoticed and do not result in sleep disruption [4]. However, most people can be awakened by a sufficiently loud noise.

Sleep physiology

Contemporary thinking regarding the physiology of sleep incorporates a two process model: the homeostatic process and the circadian process [5]. The homeostatic process is simply the balance of sleep and wakefulness. It derives from the notion that the longer you are awake, the sleepier you get. Homeostatic sleepiness increases from the time of awakening until the time one sleeps again, during which time the process is reversed. The homeostatic sleep need for humans is approximately 8 h. Hypothetically, a person could achieve their homeostatic sleep need by sleeping any time of the day or night. Essentially, the homeostatic sleep process is the body's physiological drive to get the amount of sleep required for normal, stable daytime functioning and alertness.

The circadian process, also described as the "biological clock", is more complex. Anatomically, the circadian system is located in the suprachiasmatic nuclei (SCN) of the hypothalamus above the optic chiasm. Inputs to the SCN include information regarding the photoperiod from the retinohypothalamic tract. Among the SCN outputs are other hypothalamic regions involved with the regulation of sleep and waking, as well as control of melatonin production in the pineal gland. It is responsible physiologically for the endogenous generation of normal circadian rhythmicity, which essentially keeps time for the body, and engages in the neuronal firings that instruct the various systems and organs of the body to perform, or not perform, activities appropriate to the time of day. An unencumbered human circadian clock has a daily cycle of slightly more than 24 h. Neurons in the SCN are able to maintain their 24-h periodicity through a complex gene transcription–translation feedback system. the SCN therefore relies on outside influences to determine the actual environmental time and thus resets the

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human daily cycle almost every day. The daily photoperiod is the primary influence on the timing of the circadian system.

Under most conditions, the homeostatic and circadian processes interact to produce sleep and wakefulness of appropriate duration and timing. Typically, people are alert in the morning because their homeostatic sleep drive was satisfied by sleep the previous night. It is not unusual for people to experience a dip in alertness in the early- to mid-afternoon; however, they often then feel a "second wind" of alertness and typically are the most awake and alert in the early- to mid-evening. Afternoon and evening alertness is due to the activity of the SCN in promoting an arousal signal. While the homeostatic system determines the amount of sleep needed, the circadian system optimizes sleeping during the nighttime and wakefulness during the daytime. This interplay of the homeostatic and circadian systems allows people to function well with about 16 h of daytime and evening alertness followed by approximately 8 h of reasonably consolidated sleep.

Under conditions of sleep deprivation, the circadian clock prevents meaningful recovery sleep at certain circadian phases. This suggests that the circadian clock is the more powerful influence on sleep–wake expression under these conditions. In support of this concept, researchers have found that circadian oscillation creates sleep "forbidden zones" when sleep rarely occurs, and other times when sleep is almost unavoidable [5–7]. Sleep is very unlikely to begin in the early evening, unless that person is significantly sleep-deprived. The circadian drive for sleep is most pronounced about 2 h before an individual's typical wakeup time.

Sleep stages

We also now know that sleep is characterized by two general states: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The differences between these two states are dramatic, leading some researchers to suggest that there are three normal states of brain functioning: waking, REM sleep, and NREM sleep. In normal young adults, the latter (NREM) accounts for 75–80% of total sleep time, and is composed of four stages of progressively deeper sleep. Stages one and two are referred to as "light sleep" stages from which one can be aroused easily. In stage one, electroencephalogram (EEG) tracings usually show the disappearance of the rhythmic alpha activity seen in relaxed wakefulness, and the appearance of relatively low voltage and mixed frequency patterns. There are often slow, rolling eye movements during stage one sleep, and theta waves predominate at 3–7 cycles/s. Stage one sleep will account for about 5% of total sleep in healthy young adults. In NREM stage two, sleep spindles and K complexes appear on the EEG and, coincidentally, an individual's eye motion ceases and postural control further diminishes. Most people spend the majority of their sleep in stage two.

During stages three and four, sometimes called "slow-wave sleep", "delta sleep", or "deep sleep", a person is much harder to arouse and the body is very relaxed. High-amplitude, slow delta activity dominates the EEG due to the simultaneous firing of millions of neurons driven by a pacemaker in the thalamus. In stage three sleep, delta waves make up 20–50% of the tracing, while in stage four they make up >50% [8]. These stages are determined by an examination of each 30-s epoch of sleep, according to standardized criteria.

In young adults, sleep is usually entered through NREM stage one and follows an orderly progression through the NREM stages to REM sleep. The time spent in NREM stages three and four declines with age, but REM sleep remains relatively constant. As mentioned, EEG recordings are different for the four stages, but characteristically increasing wave amplitude and decreasing wave frequency are found as one proceeds through the NREM stages. REM sleep EEG tracings mimic those found in stage one NREM sleep. A typical progression of sleep stages in a young adult is shown in Figure 1.

There are also significant somatic changes, in addition to those already mentioned, that occur during the various stages of sleep. During NREM sleep, there is a decrease in blood pressure, heart, and respiratory rate; in contrast, these functions are more active and much more irregular during REM sleep. Individuals also experience a lack of thermal regulation that leads to a decrease in body temperature during REM sleep. This can be severe enough to actually awaken a person who is so affected [2,3]. REM sleep is associated with the mental state of active dreaming, although dream-like mentation can occur during any of the sleep stages. Curiously, penile tumescence in men and analogous changes in women are normal characteristics of REM sleep.

In most cases, progression through the sleep stages is a cyclical phenomenon, with each cycle lasting approximately 90 min. During sleep, many individuals' sleep "lightens" to a point where they may briefly wake up during the night, but are then able to return to sleep and another cycle begins. There is great individual variability in these patterns, as well as in "total sleep time". Some people seem able to function adequately with five, or even fewer, hours of sleep most nights, while still others may require 10 or more hours for optimal functioning. The average sleep need is approximately 8 h; most people sleeping less than 7 h nightly actually need more.

Aging and sleep

Age is thought to have a major influence on sleep. As individuals get older, there is a marked change in their sleep patterns, with sleep becoming lighter and more fragmented, as well as less efficient (i.e. total sleep time declines as a function of total time in bed). Although the time required to

Figure 1. Typical hypnogram of sleep stages in a healthy young adult.
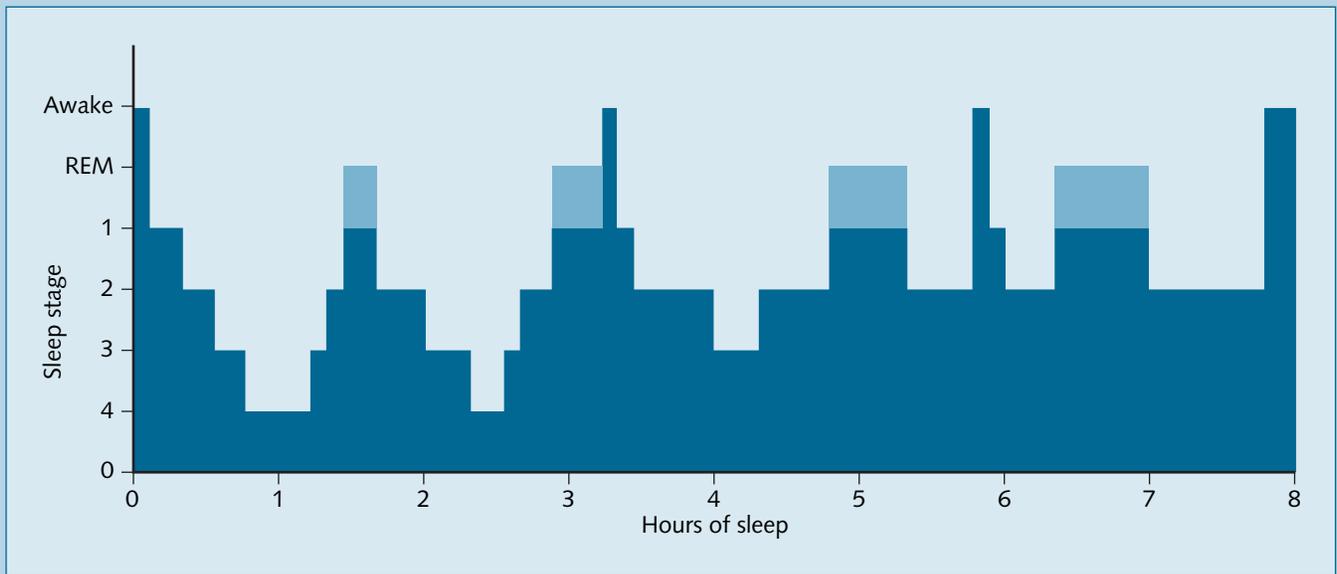
REM: rapid eye movement.

fall asleep does not differ markedly in elderly individuals from their younger counterparts, this population tend to awaken more often, and their sleep, characteristically, is not as deep [2]. This is reflected by changes in sleep stages. During the night, older individuals spend less time in stage three and four sleep and more time in stage one and wakefulness. The loss of NREM stage three and four sleep begins between the ages of 20 and 30 years, and by the age of 50 to 60 years, there may be no sleep time spent in these stages. The amount of time a person spends in deep sleep, and not necessarily the time spent in bed, is thought to be related to how refreshed they feel the next day. In addition, as we age transitions between stages one and two, and the number of awakenings and arousals, become more common, resulting in fragmented sleep. Older individuals are more likely to be sleepy during the day than their younger counterparts, and are therefore more likely to nap. This suggests that age-dependent changes reflect a reduced ability to sleep rather than a reduced need for sleep [4]. In addition to age, there are multiple other factors that influence sleep including, but not limited to, light, brain structure, and chemical compounds such as the hormone melatonin and various neurotransmitters.

Disorders of sleep

There are many reasons why an individual might not be able to achieve sufficient sleep, and in this it is very useful to differentiate sleep deprivation from insomnia. Individuals can be sleep-deprived just because they do not spend sufficient time in bed, possibly due to work requirements or lifestyle choices. We tend not to value sleep in our society; people often seem to do just about anything else before eventually getting to bed. However, individuals suffering with insomnia have ample opportunity to sleep but, for various reasons, are not able to sleep enough.

Insomnia

Insomnia can be categorized in several different ways [9,10], and is often subdivided on the basis of patterns such as its frequency (e.g. number of nights affected per week or month), duration (transient, short-term, or chronic), or whether the symptoms are "free-standing" and independent, or comorbid with some other disease state [11]. Use of the term "comorbid insomnia" has largely replaced the prior nomenclature of "secondary insomnia" [12]. This is because "secondary" implies that successful treatment of the "primary" problem will result in the resolution of the "secondary" issue. In other words, it was previously assumed that insomnia would resolve as other disorders were effectively treated; however, this is frequently not the case and treating an associated problem does not guarantee that the insomnia will resolve. Often both conditions, the primary disorder and the comorbid insomnia, must be treated independently, and sometimes aggressively.

Clinically, patients with insomnia report trouble in getting to sleep, staying asleep, or awakening too early in the morning and being unable to get back to sleep. Some nosologies also include the concept of "unrefreshing sleep" within the description of insomnia. The definition of insomnia as a disorder requires the presences of daytime impairment or consequences, such as poor concentration, irritability, memory

Figure 2. Diagram representing the opponent process, which mediates physiological sleepiness as a function of the time of day.
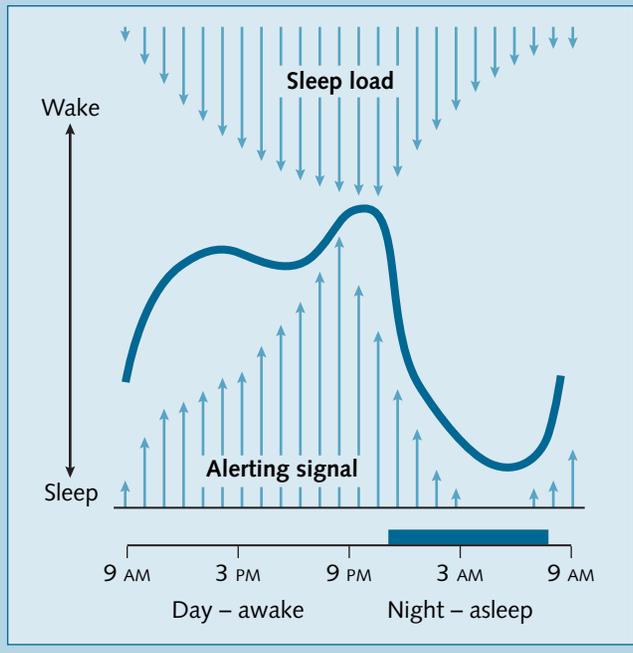
difficulty, and distress regarding the sleep difficulty [9,10]. Patients can experience one or more of the above insomnia patterns, and may have different symptoms on different nights. In addition, they can be symptom free on one night then suffer one or more symptoms the next. There may be great variability for each individual and from patient to patient. Further complicating this issue is the fact that it is difficult to assess what constitutes an adequate amount of sleep for a given individual.

Regulation of the sleep–wake cycle

As noted previously, there are many factors that influence the sleep–wake cycle. For example, light plays the major role in "setting" the circadian clock. In the morning, light strikes an individual's retina, and this sends an impulse to the SCN signaling the time of day. This results in body rhythms being reset for the next 24 h. Subjects kept in experimental settings with no windows, clocks, or other indicators of the outside time develop a sleep–wake cycle that is usually slightly longer than 24 h. This emphasizes the importance of light as it helps conform our "personal clock" to that of our environment. It also underscores the wisdom of having patients with insomnia conform to a daily routine of going to bed at approximately the same time and, perhaps more importantly, getting up at the same time in the morning. This type of routine is conducive to conforming our personal circadian clock and rhythms to that of our surroundings (Fig. 2).

Another important factor in the sleep–wake cycle is the hormone melatonin, the so-called "hormone of darkness". It is produced during the hours of darkness by the pineal gland and, following release from this gland, is involved in assisting various body systems to follow the master clock's timing. Still another entity involved in the sleep–wake process is an individual's own brain structure. It is now widely appreciated that a number of structures, housed in the hypothalamus, regulate the homeostatic sleep drive. The "wake system" is widely distributed throughout the brain, and includes the brain stem reticular activating system and other forebrain and hypothalamic regions. Thus, it can be readily appreciated that brain disruption can easily produce sleep disruption.

A number of neurotransmitters are believed to be active in sleep and wakefulness. α-aminobutyric acid, the most widely distributed inhibitory neurotransmitter in the brain, and galanin, are both concentrated in the ventrolateral preoptic nucleus (VLPO) and are believed to be involved with the switch between being awake and asleep. On the other hand, the tuberomammillary nucleus (TMN) is thought to be important for maintenance of the wake state, which is largely controlled by histamine. It is the balancing of VPLO and TMN activity that, most likely, contributes to wakefulness or sleep. Additional substances such as adenosine may contribute to sleep, while norepinephrine, serotonin, acetylcholine, and orexin/hypocretin may have a role to play in wakefulness [4].

Identifying patients with poor sleep

Questions regarding sleep should be routine in clinical practice. Asking the patient, "How much sleep do you need to feel refreshed and alert for the entire day?" and, "How much sleep do you need to stay awake even during the most soporific conditions?" may be the best way to evaluate whether or not a person is getting enough sleep [4]. Asking a partner or parent these same questions may also be beneficial.

Patients frequently do not volunteer information about their poor sleep to their doctors, and asking may be the only way that a clinician becomes aware of the issue. This can present real problems in a busy primary care practice where the practitioner is often hard pressed, in the time available, to address the various and sundry complaints that the patient actually volunteers. In a survey of 286 primary care patients, only one-third of those who reported having insomnia had ever spoken about it with their doctor, although treatment-seeking behavior did increase consistent with the severity of a patient's symptoms [13].

The Epworth Sleepiness Scale (ESS) measures daytime sleepiness, from which one can infer the adequacy of a person's sleep or the presence of a sleep disorder [14]. Individuals are asked to rate, on a scale of 1–4, how likely they are to fall asleep in eight everyday situations, such as

sitting and reading, watching television, riding in a car, or stopped in traffic. A score >10 is considered abnormal and suggests that further investigation is warranted.

Conclusion

In conclusion, good sleep is not just a nicety, but it is a necessity for an individual's quality-of-life. There is much compelling evidence reporting a bidirectional relationship between sleep and health; that is, sleep disruption is associated with an increased risk of illness, both mental and physical. Insomnia, specifically, is frequently comorbid with psychiatric disorders (depression, generalized anxiety disorder), chronic pain (arthritis, fibromyalgia), gastrointestinal disorders (gastroesophageal reflux disease), cardiopulmonary disorders (chronic obstructive pulmonary disease, chronic heart failure, asthma, sleep apnea), and neurological disorders (Parkinson's disease, Alzheimer's disease, neuropathy). In addition, many of the medications commonly used to treat these conditions can actually cause sleep disruption [2]. It is therefore essential for practitioners to not only be aware of issues specific to sleep, but also to be aware of the wider clinical implications associated with sleep disruption. Inquiring about, and aggressively managing, sleep issues will make for a healthier patient, and in the process can improve your skills as a clinician.

Disclosure

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The Challenges of Modern Day Work Schedules: Effects on Alertness, Performance, Safety, and Health

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Work schedules have evolved over the years due to the increasing demands of around-the-clock activities and technological advancements of society. As a result, individuals are often faced with work schedules that interfere with the "normal" sleep/wake cycles of nocturnally placed sleep and daytime work. Work schedules that oppose this natural biological rhythm result in physiological disruptions leading to sleep loss, degraded performance and mood levels, and increased risks to health and safety. It is estimated that nearly 15 million Americans work non-traditional hours for numerous reasons ranging from increased work demands to increased time for family or social activities. While service-oriented occupations (e.g. healthcare, public safety, transportation) tend to be more commonly associated with shift work, non-standard schedules also exist in modern conveniences (e.g. leisure, hospitality services) and highly technological environments (e.g. energy, nuclear power plants). Individuals reporting insomnia or excessive sleepiness in relation to a work period that occurs during the habitual sleep phase may be diagnosed with shift-work sleep disorder (SWSD). SWSD is classified as a circadian rhythms disorder and it is estimated to affect 10% of those employed in shift work. Both non-pharmacological and pharmacological approaches have been identified for the management of the effects of SWSD. A comprehensive management program that involves, for example, a shared responsibility between both the individual and organization is essential for addressing the risks associated with around-the-clock work schedules. Effective management of modern work schedules at both an individual and organizational level offers an opportunity for sleep medicine to improve the health and safety of society. *Int J Sleep Wakefulness – Prim Care* 2007;**1**(1):7–13.

Work schedules in modern day society

Around-the-clock activities required in today's society often result in shifted work schedules that interfere with "normal" sleep/wake cycles of nocturnally placed sleep and daytime work. Although shift work has traditionally included only night work and rotating shift schedules, the modern definition is more comprehensive and has been expanded to include any schedule that can potentially affect both sleep and circadian rhythms. Specifically, any work undertaken outside the traditional 7 AM–6 PM time frame can be categorized as shift work [1]. Table 1 identifies some of the common scheduling factors that disrupt sleep and circadian rhythms, subsequently affecting alertness and performance [2].

According to the US Bureau of Labor Statistics [3], nearly 15 million Americans work alternative shifts outside traditional work hours, including evening shifts (4.7%), night shifts (3.2%), employer-arranged irregular schedules (3.1%), rotating shifts (2.5%), and other non-daytime schedules (1.3%). This comprises approximately 15% of the overall, full-time working population, and it is expected that the number of people working shifted schedules will rise as around-the-clock operations continue to become more common and increasingly accepted as the standard for any work environment.

Shift-work schedules are not unique to a single environment and exist in multiple work settings, extending from service occupations to highly technological and safety sensitive settings (e.g. energy and nuclear power plants). The prevalence of shift work is greatest amongst service occupations, such as the protective services, food preparation/serving, and production/transportation/material moving occupations, with leisure and hospitality industries having the greatest proportion of shift workers [3]. The expectation that humans can adapt to any schedule, at any time of the day, while continuing to maintain high alertness and performance levels will become more common,

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Table 1. Work-schedule factors that affect sleep, circadian rhythms, and alertness [2].

- Early start times
- Extended work periods
- Amount of work time within a shift or duty period
- <8 h off between work periods
- Number of consecutive work periods
- Insufficient recovery time between consecutive work periods
- Night work through window of circadian low
- Daytime sleep periods
- Day-to-night or night-to-day transitions (schedule stability)
- Changing work periods (e.g. starting and ending times, cycles)
- On-call or reserve status
- Schedule predictability (i.e. available in advance)
- Time zone changes
- Unplanned work extensions

especially since service-providing industries are expected to account for the most new jobs (estimated at 18.7 million of the 18.9 million new wage and salary jobs generated over 2004–2014 period) [4]. However, it is thought that people working non-traditional schedules are more likely to suffer from disturbed sleep and on-the-job sleepiness, and will never fully adapt to their work schedule [1,5]. As a result, physicians can expect to see an increase in the number of patients complaining of difficulties in coping with shift work schedules and experiencing decrements in both mental and physical functioning.

Interestingly, the main reason given by shift workers for working non-daytime schedules is that it is the "nature of the job" [3]. Other reasons include increased work demands and variability in scheduling allowing for more continuous days off and thus increased time for family or social activities. Furthermore, a non-traditional schedule is desirable for some when the timing of the shifted work schedule is opposite to the schedules of other working family members. This schedule flexibility allows the individual to attend to family needs such as childcare and household responsibilities. Additionally, some employers offer an added monetary incentive for non-standard work schedules.

Effects of shift work
Physiological disruption
When people consider the challenges associated with shift work, sleep difficulties are typically one of the first issues identified, since the majority of shift workers complain of disturbed sleep and overall sleepiness [5]. Many believe that

if they can "get a handle on their sleep schedule", then all of the other problems associated with shift work would be alleviated. However, adapting to shift work is a more complex issue.

Humans are hardwired to function as diurnal animals with sleep occurring during the nighttime hours. Sleep is most consolidated and efficient when initiated near the rising phase of the melatonin rhythm, which typically occurs during the nighttime hours [6]. However, sleep periods of shift workers more commonly occur when the body is programmed to be awake [7]. There is, consequently, a disruption of the sleep/wake cycle forcing these individuals to override the endogenous biological clock, the circadian pacemaker, which programs them for daytime activity and nighttime sleep. Thus, overall sleep is disrupted with shift workers complaining of both initial (difficulty falling asleep) and middle (difficulty staying asleep) insomnia, although middle insomnia is more frequently reported [1]. This results in the shift worker experiencing continuous partial sleep loss, which can accumulate into a chronic state of sleep deprivation. Some individuals continue to report sleep difficulties, including longer sleep latencies when trying to fall asleep and waking before their desired "wake" time, even after returning to a "standard" schedule [8].

Unlike fixed-day schedules, where work report times typically occur within a few hours of awakening, shift workers are further challenged if they are unable to obtain consolidated periods of recovery sleep within close proximity to starting work. Therefore, the duration of wakefulness before reporting for scheduled work duty is another factor to be considered by shift workers. The longer a person remains awake, the sleepier one becomes [9]. This accumulation of fatigue across the waking hours can then extend into the duty period itself. If the individual keeps a fixed non-standard schedule, sleepiness levels can continue over successive days or weeks and the individual is likely to accumulate a sleep debt [10].

Shift work is also associated with circadian disruption due to the misalignment between the phase of the circadian pacemaker and the sleep/wake cycle. The circadian pacemaker is located in the suprachiasmatic nuclei (SCN) of the hypothalamus and contributes to the control of waking alertness and performance and timing of sleep periods in an approximately 24-h sinusoidal rhythm [11]. On a typical 24-h cycle, with sleep nocturnally placed, performance and alertness variables reach a low point during a trough occurring in the early morning (around 5 AM); a second trough, of lesser extent, is observed in the late afternoon and is often referred to as the post-lunch dip [12]. However, in those working non-standard schedules the circadian system becomes desynchronized; it no longer follows a

regular 24-h pattern and becomes unpredictable. Competing exogenous factors, or zeitgebers (i.e. time givers), from the day/night cycle and a day-oriented society continually push a non-standard schedule back towards its usual diurnal orientation. The most powerful zeitgeber is the light/dark cycle.

It is the light/dark cycle that is largely responsible for entraining circadian rhythms to a 24-h day [6]. Light information is transmitted through a retino-hypothalamic tract to the SCN of the hypothalamus, which is the location of the circadian pacemaker. Therefore, light acts as a powerful stimulus in the regulation of circadian rhythms, contributing to a stable phase relationship between circadian rhythms and the external 24-h day [6]. The light/dark cycle of a day-oriented society, with sleep nocturnally placed, is in direct opposition to the shift-work cycle. In laboratory settings, controlling light/dark exposure to mimic cycles associated with shift work (i.e. light at the subjective night and dark during the subjective day) should promote adaptation to working at night and sleeping during the day; however, conflicting light/dark signals and social interactions during actual 24/7 operations prevent circadian adaptation. Thus, shift workers rarely adapt fully to their work schedule.

Overall, the sleep/wake cycles of shift workers are constantly altered between work days and non-work days. The demands of work scheduling drive the scheduled sleep/wake times on work days. However, on non-work days, shift workers tend to revert to a daytime schedule. This schedule change is influenced by the physiological need for recovery sleep during night time hours as well as domestic factors of social and family obligations [1].

Performance changes

The inherent nature and mechanisms of the circadian clock allows only a gradual re-entrainment process when working a shifted schedule. Conflicts between the endogenous circadian system and environmental time cues affect this re-entrainment and those working shifted schedules are not able to adapt to schedule changes quickly. As a result, they experience performance and physiological changes that occur in a manner that is unpredictable [11], and can be seen within as little as 2 h of sleep loss [13]. Performance levels and sleepiness are worsened due to the effects of sleep loss and to the difficulties associated with maintaining alertness and high cognitive functioning at an adverse circadian phase. This is of concern since maintaining optimal performance and alertness levels in a work setting is critical to maintaining safety.

When regular 24-h sleep/wake cycles are maintained and sleep is protected, neurobehavioral performance tests do not demonstrate significant diurnal variation during waking hours

from 1–2 h after awakening to 1–2 h before sleep onset [14]. However, research has shown that significant decreases in neurobehavioral performance can occur when sleep/wake patterns are disrupted or when work times are scheduled several hours before or after peak circadian performance levels. These changes include [15–17]:

- Slowed reaction times.
- Cognitive slowing.
- Deficits in frontal lobe functioning.
- Degradations in response accuracy and sleep.
- Short-term memory difficulties.

Decrements in neurobehavioral functioning are especially apparent during late night and early morning hours [18].

An increased occurrence of work-related injuries has been associated with extended work days, especially during night shifts [19]. For example, the near melt-down at the Three Mile Island (Harrisburg, PA, USA) nuclear power plant on March 28, 1979, occurred during the early morning hours of 4–6 AM. The individuals failed to detect the loss of core coolant that resulted from a stuck valve in one of the unit reactors [20,21]. The catastrophe at the Chernobyl (Ukraine) nuclear plant also occurred during the early morning hours (around 1 AM) and again was attributable to human error [22,23]. These two examples of the failure to monitor processes accurately are partially attributable to working at an adverse circadian phase and with an accrued sleep debt. These work-related incidents and accidents have not only been observed in highly technological environments, but also seen in everyday activities including driving and medical services [2,18].

Another common response observed in those undertaking shift work is uncontrollable sleepiness, in which individuals have no voluntary control over falling asleep and commonly experience microsleeps (short, uncontrollable episodes of sleep) [24,25]. Such involuntary sleep periods affect safety not only during work periods but also during the drive to and from work [26]. Individuals working non-standard schedules are more likely to have a higher exposure to nighttime driving, increasing the chances of drowsiness while driving and decreasing the ability to effectively respond to stimuli or emergency situations. In fact, research has demonstrated that the odds of falling asleep or being involved in an accident while driving are doubled for rotating shift workers [27].

Adverse mood and health effects

Although individuals report increased sleepiness with the progression of sleep loss, research has shown that these subjective estimates are unreliable; generally, humans are

Table 2. Health and safety risks associated with shift work.

Health effects
- Increased risk of heart disease
- Increased risk of breast cancer in women
- Gastrointestinal difficulties
- Psychological stress
- Increased sick days
- More likely to smoke and/or use alcohol
- Disruption in family/social time
- Decreased quality of life
- Shift-work sleep disorder

Neurobehavioral
- Accuracy and speed degradation
- Narrowing of attention
- Unable to integrate information
- Impaired logical reasoning
- Decreased attention span
- Decreased cognitive performance
- Microsleeps

Subjective
- Increased subjective fatigue ratings
- Mood deteriorations
- Acceptance of lower standards

sleepier than they report [25,28]. Therefore, an individual working a non-standard schedule is not likely to be aware of increasing sleepiness levels. For example, if an individual is in a highly engaged environment, involving physical activity or interaction with other individuals, the underlying sleepiness may not be as noticeable and that person may rate themselves as being more alert than their physiological responses would indicate.

Fatigue can also affect overall mood (See Table 2). Sleepy individuals often show deteriorations in mood and are less able to communicate and interact socially with others [17,29]. The effects of shift work on overall mood are experienced not only by the person working the non-standard schedule but can extend to their family and/or friends. A continuous challenge faced by shift workers is the requirement to be awake and active when most people are sleeping and then to sleep when others are awake. This can result in decreased social and family activities, which can in turn result in a more negative mood and increased depression [30].

In addition, adverse health effects are more frequently seen in shift workers (Table 2). Although the specific underlying causes and mechanisms are not firmly established, possible explanations include, but are not limited to, chronic circadian misalignment and digestive responses being out of synchronisation with the circadian phase. These adverse health effects include increased risk of heart disease, occurrence of gastrointestinal difficulties, risk for breast cancer in women, ringing in the ears, and a two-fold greater rate of gastric ulcers compared with non-shift workers; these effects can be long term [30–33]. Furthermore, it has been reported that night shift workers are 62% more likely to smoke and have a 40% increased use of alcohol compared with non-shift workers [34]. The use of these two substances can further contribute to sleep difficulties. Additionally, sleepiness associated with shifted schedules can have both direct and indirect costs in the workplace, with increases in absenteeism and work accidents.

Shift work sleep disorder
Prevalence
A subset of shift workers report insomnia when trying to sleep and excessive sleepiness during waking hours, no matter how much sleep they obtain. Individuals in whom these symptoms persist may be suffering from a condition known as shift-work sleep disorder (SWSD). Those who have a strong need for stable sleep and wake times are particularly vulnerable to SWSD.

The prevalence of SWSD varies depending on the occurrence of shift work within a specific population. A recent study estimated that 10% of the shift-work population suffers from SWSD [30]. Of an estimated 15 million shift workers in the US, nearly 1.5 million may be affected by SWSD [30]. However, the same study also found that up to 32% of shift workers experience symptoms of insomnia or excessive sleepiness (the minimum criteria for SWSD), thus the prevalence of SWSD might in fact be closer to 5 million. It is believed that the rate of SWSD will continue to rise with increasing advances in modern technology [1].

Diagnosing SWSD
According to the International Classification of Sleep Disorders, SWSD is a disorder of the circadian rhythms characterized by symptoms of insomnia and excessive sleepiness that occur in relation to work schedules [35]. The lack of adaptation to a work/rest schedule results in loss of a normal sleep/wake cycle. Consequently, sleep is not fully restorative and individuals can experience significant amounts of sleep loss [35]. Although SWSD is defined as a circadian rhythms disorder, it is more complex and can be considered a combination of three factors [1]:

- Sleep.
- Circadian.
- Domestic.

Table 3. Summary of diagnostic criteria for shift-work sleep disorder according to the American Sleep Disorders Association [35].

1. The patient has a primary complaint of insomnia or excessive sleepiness.

2. The primary complaint is temporally associated with a work period (usually night work) that occurs during habitual sleep phase.

3. Polysomnography and the Multiple Sleep Latency Test demonstrate the loss of a normal sleep/wake pattern (i.e. disturbed chronobiological rhythmicity).

4. No medical or mental disorder accounts for the symptoms.

5. The symptoms do not meet criteria for any other sleep disorder producing insomnia or excessive sleepiness (e.g. time-zone change [jet lag] syndrome).

Table 4. Sample questions for the diagnosis of shift-work sleep disorder.

1. Does the patient report:
   a. excessive sleepiness or difficulty staying awake during routine tasks (e.g. reading, watching television, or driving)?
   b. excessive sleepiness interfering with work-related tasks?

2. What is the patient's work schedule? Does it overlap with habitual sleep time (i.e. work schedule occurring between 6 PM-7 AM)?

3. During what time frame does the patient normally sleep?

4. Does the patient meet diagnostic criteria for any other sleep disorders associated with excessive sleepiness or insomnia?

5. Does the patient suffer from any other medical or mental disorder associated with excessive sleepiness?

The affected individual suffers from sleep loss, circadian disruption, as well as a degree of domestic/social isolation due to the non-standard schedule. The five criteria defined by the American Sleep Disorders Association for the diagnosis of SWSD are summarized in Table 3 [35].

The minimal criteria for diagnosing SWSD are primary complaints of both insomnia and excessive sleepiness associated with a work schedule that occurs during the habitual sleep phase. If these two criteria are met, there is justification to evaluate the patient's sleep/wake history to further explore the existence and severity of SWSD. A sleep specialist can measure polysomnographic activity during the shifted sleep period as well as monitor levels of sleepiness during regular waking hours using the Multiple Sleep Latency Test (MSLT).

Based on these diagnostic criteria, the severity of SWSD can be categorized as mild, moderate, or severe [35]. Mild forms of SWSD are associated with 1–2 h of sleep loss per day, with individuals taking 10–15 min to fall asleep on the MSLT (normal range of MSLT scores in healthy adults is 10–20 min). Although those suffering from moderate forms of SWSD also report daily insomnia, excessive sleepiness is reported to interfere with daily workplace performance and activities that require a certain level of attention, such as driving. Sleep loss for these individuals is approximately 2–3 h/day, with MSLT scores in the 5–10-min range. Severe forms of SWSD result in extreme levels of excessive sleepiness and it is not uncommon for the individual to fall asleep during social or physical activities. The daily complaint of insomnia, associated with >3 h of sleep loss per night, is associated with severe social and operational performance decrements. These individuals tend to fall asleep in <5 min.

Table 4 lists a number of sample questions that can be used by physicians as a starting point when assessing a patient for SWSD.

Treatment options

Increasing total sleep time and ensuring ample recovery sleep are the main management goals for sleep loss associated with working non-traditional schedules or SWSD. These can be achieved through both non-pharmacological and pharmacological approaches. The most common non-pharmacological options include:

- Strategies to help increase total sleep times.
- Strategic napping.
- Appropriately timed bright light exposure.

Developing pre-bedtime routines, optimizing the sleep environment (e.g. eyeshades to create a dark environment, earplugs to reduce noise levels), and keeping stable sleep/wake cycles are relatively simple strategies that can help individuals maximize their total sleep amounts. Strategic napping is an effective strategy that can be used to maximize the total amount of sleep obtained within a 24-h period [25]. Napping prior to a scheduled duty period reduces the number of continuous hours awake and can also be used during a low workload portion of the duty period or the circadian low point to help improve alertness and performance over a short period of time [25]. Appropriately timed exposure to, and avoidance of, bright light can have both alerting and shifting benefits [6]. Specifically, avoidance of light immediately after a work period and prior to a sleep period can help individuals adapt to shift work [36]. For example, wearing sunglasses on the commute home and going to bed in a darkened room shortly after a work period are simple strategies to avoid bright light and promote adaptation. Additionally, exposure to light during the night shift not only has a direct alerting affect but will also

promote adaptation to the shifted sleep schedule. However, as light of a specific quantity and duration can shift the circadian rhythm to an earlier or later time, caution should be used to ensure that the level of light exposure has the desired effect.

Pharmacological approaches used to assist those in management of their SWSD include:

- Caffeine.
- Hypnotics.
- Melatonin.
- Modafinil.

Caffeine is the most widely used wake-promoting agent [37]. However, it is important to be aware of the individual differences associated with the effective dose and duration of effect. Hypnotics have a short half-life and can be used to increase daily sleep amounts. However, all of the standard cautions (e.g. lowest effective dose, used for shortest amount of time, monitoring of effectiveness and adverse effects) associated with hypnotic use should be considered. Research has shown that melatonin can be used as an effective aid in altering the circadian rhythms for shift workers [38]. Modafinil, which has been approved as a wake-promoting medication by the US Food and Drug Administration, can be used to treat excessive sleepiness associated with SWSD. It has been shown to increase alertness and improve performance and clinical symptoms when taken 1 h prior to a scheduled work period [39].

In some cases use of a single treatment option will be effective, but with more severe levels of SWSD a combination of approaches might be required. However, the effectiveness of specific treatment approaches is determined by individual differences [1]. Not all individuals will react in the same manner and/or over the same time to a single or combination of strategies.

Addressing the performance, health, and safety risks associated with shift work is a complex issue. One effective approach is a comprehensive alertness management program involving a shared responsibility between the individual and organization [2,40]. Individual efforts could focus on obtaining information on the topics of sleep loss, circadian disruption, sleep disorders, and potential alertness strategies, while organizations could facilitate education and evaluate the role of schedules. Without an accepted shared responsibility, it is likely that efforts to manage the risks will not be effective.

More importantly, both individuals and organizations play a role in the diagnosis and treatment of sleep disorders. It is important for individuals to be aware of the symptoms of SWSD and potential treatment options, as well as to remain compliant with prescribed treatments. Furthermore, organizations should provide information on SWSD and develop policies that support individuals diagnosed with this condition.

Conclusion

As technology continues to develop and evolve in our increasingly 24/7 society, a growing number of individuals will be faced with working schedules outside of "normal" daytime hours. The timing of their sleep/wake schedules deviates from the normal cycle of nocturnally placed sleep and daytime work and commonly fluctuates between work and non-work days. This sleep and circadian disruption combined with conflicting light and social cues contribute to individuals not adapting fully to a shift work schedule. As a result, performance is significantly degraded and there are increased risks to both safety and health, with consequent increases in the risk of sleepiness-related incidents and accidents.

It is not uncommon for shift workers who keep these non-standard schedules to suffer from SWSD, varying from mild to severe forms. Using specific criteria, sleep specialists can diagnose the existence of the SWSD and can work with patients to prescribe a treatment regimen including both non-pharmacological and pharmacological options to help manage their challenges with insomnia and excessive sleepiness during waking hours. When assessing the benefits of an effective treatment approach, it is also important to consider individual differences in how patients respond as well as the limitations of the overall approach.

Managing modern work schedules at the individual level, through diagnosis of medical conditions and specific treatment regimens, is only one component in addressing performance, health, and safety challenges associated with shift work. A comprehensive approach that includes organizational level involvement and a shared responsibility with individuals offers an even greater opportunity for sleep medicine to improve the health and safety of society.

Disclosures

The authors have no relevant financial interests to disclose.

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The Interactions Between Sleep, Metabolism, and Obesity

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We are currently facing an obesity pandemic for which there are no easy solutions. This is because the factors that have contributed to this pandemic are complex and incompletely understood. One contributing factor that has attracted much interest is shorter sleeping hours. Several large epidemiological studies of adults and children from different countries have demonstrated an association between short sleep duration and obesity. From the Wisconsin Sleep Cohort Study and sleep laboratory studies, the mechanisms for this association may include alterations in the circulating levels of several metabolic hormones (leptin, ghrelin, cortisol, insulin, and growth hormone) that could result in increased appetite and changes in body weight and composition. Short sleep duration may also alter energy expenditure. Although the full mechanisms for the association between short sleep duration and obesity are currently under investigation, it can be argued that encouraging adequate sleep should be added to other lifestyle measures to help prevent obesity. *Int J Sleep Wakefulness – Prim Care* 2007;**1**(1):14–23.

The precise physiological functions of sleep remain to be determined, but it is increasingly being recognized that sleep plays a significant role in maintaining our physical and psychological well-being [1]. This is because several large epidemiological studies have identified important contributions of sleep to various health outcomes and mortality. Simultaneously, there has been a shift in sleep research from concentrating on the brain and neurocognitive effects of sleep loss to investigating the impact of sleep on other organs and on global physiology.

This has been accompanied by more "real-life" experimental paradigms aiming to unravel the mechanisms involved, i.e. studies on the effects of chronic partial sleep loss instead of acute total sleep deprivation. In addition, there is now substantial interest in determining the characteristics of individuals who lie at the extremes of sleep duration: the "short" and "long" sleepers [2]. These simultaneous advances in sleep research have highlighted the possibility that alterations in sleep duration could result in metabolic changes that may contribute to the development of obesity, insulin resistance, and cardiovascular disease [3–24]. The objective of this review is to examine the evidence for an interaction between sleep duration and obesity and to discuss the potential metabolic mechanisms involved.

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The burden of obesity

Obesity is a global public health problem [25]. A recent report from the World Health Organization estimated that, in 2005, >1 billion people worldwide were overweight and >300 million were obese [26]. The report forecasts that the number of overweight individuals will reach 1.5 billion by 2015. In the US and other western countries, obesity is expected to become the most common preventable cause of death [27]. Most alarming has been a dramatic rise in the number of children who fit the criteria necessary for the diagnosis of obesity, not least because childhood obesity tracks into adulthood [28]. Data from the Center for Disease Control and Prevention in the US show that the prevalence of children aged 6–19 years old who were considered to be overweight increased from 4–5% in 1963–1970 to 15% in 1999–2000 [29]. Major contributors to the morbidity and mortality associated with obesity include concomitant insulin resistance, type 2 diabetes mellitus, sleep-disordered breathing, and cardiovascular disease [25].

Although there is a strong genetic contribution to obesity, it is believed that the current obesity pandemic is largely driven by environmental factors that alter the balance between energy intake and energy expenditure. Unfortunately, current interventions aimed at altering food selection (with different diets encouraging alterations in different macronutrients) and calorie intake (e.g. smaller portions), and increasing physical activity, have not resulted in long-term weight loss and maintenance. This is because our understanding of factors that influence individuals to choose and over-consume

Figure 1. Percentage of US adults sleeping 6 h per 24-h period in 1985 and 2004 by age and sex group.
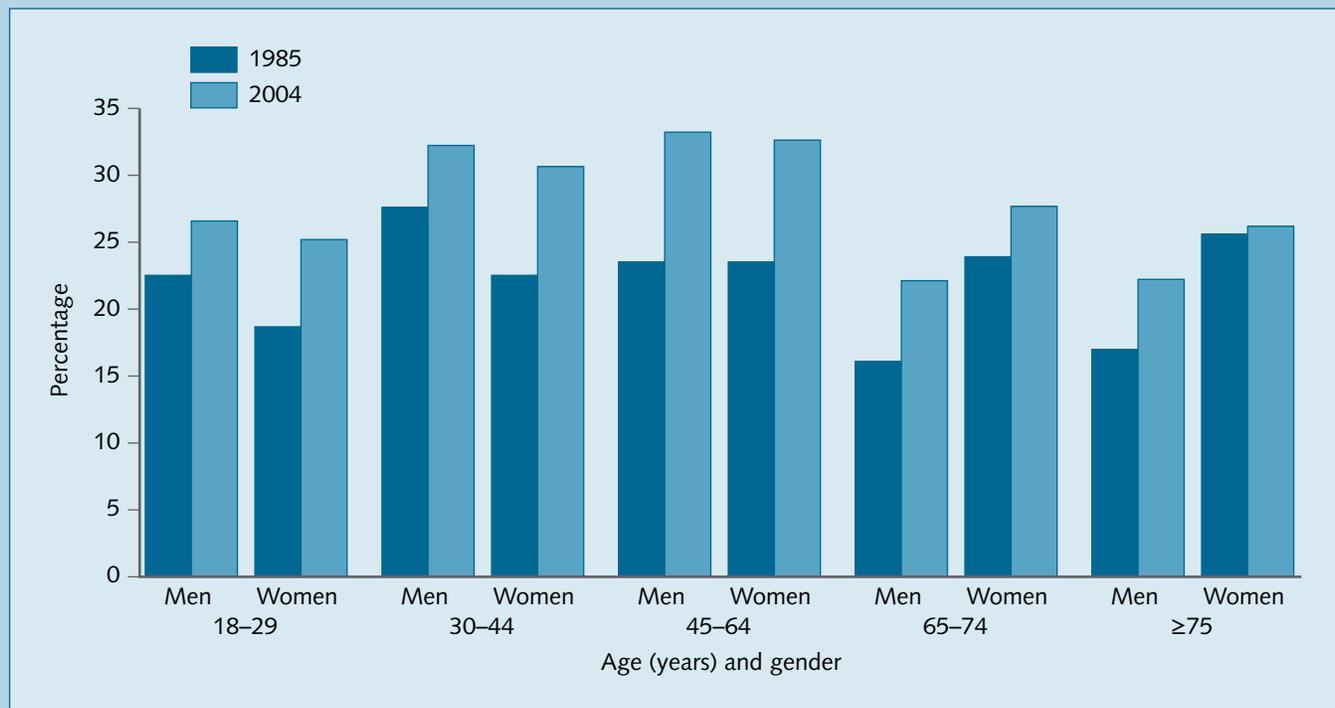
Adapted with permission from [28].

particular foods, affect a person's desire/ability to undertake physical activity, and help maintain long-term motivation needs to be improved. Although there are insufficient robust data from children, data from adults in the US suggest that the trend in obesity has coincided with a trend in shorter sleeping hours (Fig. 1) [30]. This may be a coincidence, but several sources of evidence suggest that sleep may affect both sides of the energy balance equation, resulting in obesity.

Population studies link sleep duration with obesity
Several large population studies have identified a significant dose–response relationship between short sleep duration, obesity, and metabolic disturbances across all age groups and several ethnic groups [3,5–24,31,32]. The studies in children and adolescents have recently been summarized and reviewed [21]. Table 1 lists the studies in adults and their key findings. Interestingly, several studies in adults report a U-shaped relationship between sleep duration and body weight, suggesting that both short and long sleepers are susceptible to obesity. Some studies have suggested that there are differences in the sleep duration–obesity relationship in males and females. Importantly, there are now several prospective studies reporting an association between short sleep duration and obesity. While it has been argued that the impact of short sleep duration on body weight is small, this does not equate

with being biologically meaningless. In the Wisconsin Sleep Cohort Study (WSCS) population [20], for example, a loss of 3 h of sleep from a baseline of approximately 8 h was associated with an average 4–5% higher body weight – this difference being comparable to the average weight loss that can be achieved with lifestyle changes or any of the currently available anti-obesity drugs [33]. Similar differences in body weight have been reported from a longitudinal study of young adults [9]. Since weight gain is associated with only a minor daily energy excess (as little as 100 kilocalories), and we know that even modest reductions in body weight (5–10%) can reduce the complications of obesity such as type 2 diabetes [34], the change in body weight with shorter sleep is likely to be clinically meaningful. Although the relationship between sleep and body weight is U-shaped in older adults, a clear negative linear relationship between sleep duration and body mass index (BMI) has been seen in large, more homogeneous studies of young adults and children [21]. This sleep–obesity association has been consistently observed and has been shown to be independent of potential confounders such as television viewing and self-reported physical activity. Importantly, a recent large birth cohort study from the UK, the Avon Longitudinal Study of Parents and Children (also called "Children of the 90s") has identified that short sleep duration at an early age of 30 months predicts obesity at age 7 years [21,32]. Given that sleep is important in neurodevelopment,

Table 1. Summary of epidemiological studies reporting associations between sleep duration and obesity in adults.

Study	Country	n	Design	Key findings
Vioque et al., 2000 [22]	Spain	1772	Cross-sectional	Prevalence OR for obesity 0.43 (95% CI 0.27–0.67) for sleeping ≥9 h vs. ≤6 h; prevalence OR for obesity was 24% lower for each additional sleeping h/day.
Shigeta et al., 2001 [18]	Japan	437	Cross-sectional	Sleeping ≤6 h was associated with BMI ≥25 kg/m^2 (OR 1.98, 95% CI 1.03–3.82) vs. >6 h sleep.
Kripke et al., 2002 [12]	USA	1.1 million	Epidemiological survey; Cancer Prevention Study II	U-shaped relationship between sleep duration and obesity in women, but linear relationship for men from baseline sleep duration of 7 h.
Heslop et al., 2002 [10]	UK	6797 (baseline)	Cross-sectional analysis from cohort study	Short sleep duration associated with obesity at baseline and at second screening.
Taheri et al., 2004 [20]	USA	721	Cross-sectional; Wisconsin Sleep Cohort Study	U-shaped relationship between sleep duration and obesity; short sleep duration was associated with higher ghrelin and lower leptin levels.
Cournot et al., 2004 [7]	France	3127	Cross-sectional; Vieillissement et Santé au Travail study	Mean BMI was higher in women reporting sleep duration <6 h vs. ≥6 h (24.4 kg/m^2 vs. 23.4 kg/m^2); no association in men.
Patel et al., 2004 [14]	USA	82 969 (women)	Prospective; Nurses Health Study	U-shaped relationship between sleep duration and BMI in women
Hasler et al., 2004 [9]	Switzerland	496	Prospective; Zurich Cohort Study	Trend for negative association between average change in weight gain and average change rate in sleep duration.
Vorona et al., 2005 [24]	USA	924	Cross-sectional, primary care center-based	Overweight and obese patients slept less than those of normal weight.
Gangwisch et al., 2005 [8]	USA	9588	Cross-sectional; National Health and Nutrition Examination Survey	Those aged 32–49 years who slept <7 h had a higher BMI vs. those who slept ≥7 h.
Singh et al., 2005 [19]	USA	3158	Cross-sectional, telephone interview	U-shaped relationship between sleep duration and obesity, but only significant for shorter sleep hours.
Patel et al., 2006 [16]	USA	68 183 (women)	Prospective; Nurses Health Study	Women sleeping ≤5 h/day gained 1.14 kg and women sleeping 6 h/day gained 0.71 kg more than those sleeping 7 h/day over 16 years, no relation between sleep duration and calorie intake or reported physical activity.
Kohatsu et al., 2006 [11]	USA	990	Cross-sectional survey, rural population	Weeknight self-reported sleep duration negatively correlated with BMI (beta=−0.42; 95% CI −0.77 to −0.07).

BMI: body mass index; CI: confidence interval; OR: odds ratio.

it can be hypothesized that short sleep duration at a young age may somehow alter the brain's hypothalamic appetite circuitry. Other studies have identified associations between sleep duration, insulin resistance, diabetes mellitus, and increased cardiovascular risk [4,31].

The association between short sleep duration, metabolic hormones, and appetite

Most population studies have relied on self-reported sleep duration rather than objective measures, suggesting that the association between sleep duration and obesity may not be truly accurate i.e. time in bed does not equate with time asleep and does not take into account any sleep disturbance. Reported sleep measures are likely to be most accurate for children due to parental reporting [35,36]. So far, there has only been one study using short-term actigraphy in adolescents to objectively determine sleep duration and disturbance and their interaction with obesity [37]. Additionally, it may be argued that the association between short sleep duration and changes in body weight is a

Figure 2. Leptin and ghrelin in appetite regulation. Leptin is released by adipocytes and signals the extent of fat stores to the hypothalamus; it is involved in longer-term regulation of appetite and energy expenditure. Low leptin appears to be a much more powerful signal in stimulating appetite since obesity is associated with high leptin and leptin resistance. Leptin is transported into the hypothalamus from the circulation and it is believed that defects in this transport mechanism are responsible for leptin resistance in obesity. Ghrelin is released by the stomach. It undergoes a unique post-translational modification by the addition of an octanoyl fatty acid group, which is essential for biological activity. It is possible that the fatty acid group may also facilitate passage across the blood–brain barrier. Other hormones that may be important in appetite regulation are peptide tyrosine tyrosine, other gut peptides, and adipocytokines.
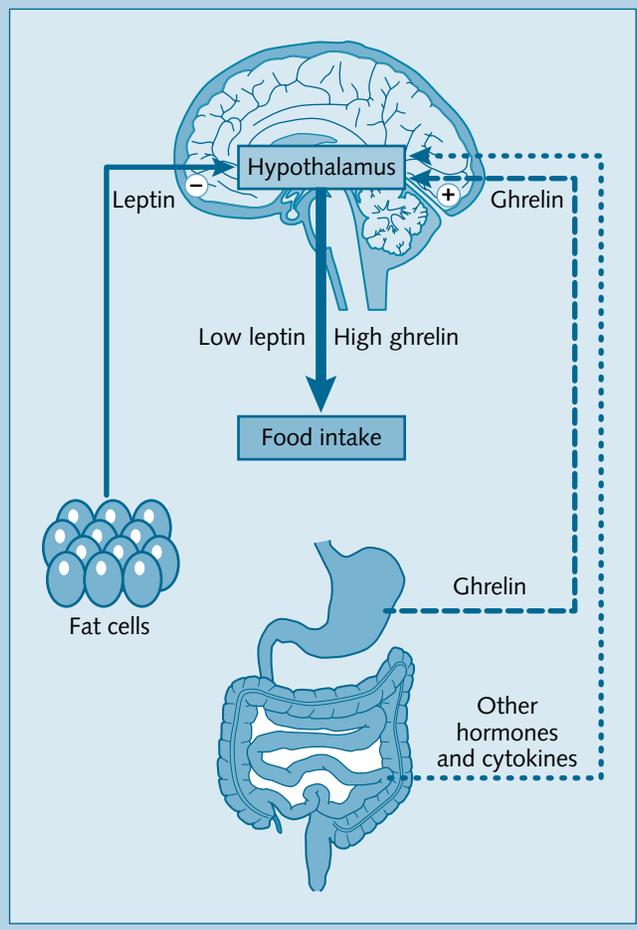
adults and children also suggest that short sleep duration may precede the development of obesity [16,38]. It is likely that different mechanisms operate in the sleep–obesity link in adult long sleepers compared with short sleepers; therefore, further study of long sleepers is necessary.

There are bidirectional interactions between several hormones and circadian and homeostatic sleep mechanisms. The release of hormones may be tied to sleep (e.g. growth hormone secretion during slow-wave sleep), transitions between sleep stages (e.g. plasma renin activity having troughs during rapid eye movement [REM] sleep and peaks in non-REM [NREM] sleep), and transitions between sleep and wakefulness (e.g. cortisol being highest on awakening). Additionally, hormones have an effect on sleep in their own right. In the WSCS, it was hypothesized that the link between short sleep duration and obesity could be mediated by alterations in circulating leptin and ghrelin levels, two opposing hormones in appetite regulation (Fig. 2) [20,39].

Leptin is a 16 kDa, 167 amino acid, secreted protein that is primarily produced by adipose tissue [39–42]. The rate of leptin secretion and its plasma concentration are correlated with total fat mass. Considerable information has been gained about the various physiological functions of leptin by examining differences between wild-type rodents and their counterparts with single gene mutations causing either the suppression of normal leptin production or the expression of dysfunctional leptin receptors. These mutant animals are hyperphagic, exhibit obesity, and are usually insulin resistant. In the few humans with leptin system gene mutations, the greatest impact of leptin deficiency appears to be on appetite rather than energy expenditure [43].

Leptin is an important peripheral signal that allows the organism to maintain body weight at a particular set point despite daily fluctuations in food intake and energy expenditure. In starvation, leptin levels fall, resulting in activation of hypothalamic neuronal circuits that adapt energy intake, energy expenditure, and behavior such that loss of fat mass is minimized. Weight gain results in increased leptin levels that act on the hypothalamic neuronal circuitry to induce a reduction in fat mass. Excessive weight gain is associated with adipose tissue expansion and high circulating leptin levels. It has been proposed that, in obesity, a defect in the transport mechanism of leptin into the central nervous system may occur, resulting in the observed leptin resistance. Therefore, low leptin levels in states of energy deficit are a greater biological signal than high leptin levels [41]. Weight loss results in leptin deficiency and, interestingly, adaptations to reduced body weight are reversible with low-dose leptin administration [44,45].

Leptin circulates bound to a soluble receptor. As well as food intake and changes in energy balance, leptin levels are

spurious or a surrogate marker for another factor that impinges on body weight regulation. However, in addition to the extensive epidemiological data suggesting a link between short sleep duration and obesity, recent evidence has begun to suggest a mechanistic link involving metabolic hormones. Emerging evidence from longitudinal analyses in

regulated by several factors, including negative regulation by the sympathetic nervous system [46]. Levels of leptin, but not its soluble receptor, show circadian changes; they are low during the day but rise in the night during sleep (leptin levels peak at about 2 AM). Although the leptin amplitude is diminished in parenterally-fed individuals, this rhythm is not eliminated [47]. The diurnal leptin pattern has been reported to mirror changes in body temperature and parallel plasma insulin and glucose levels. In obese individuals, there is a sharper rise in leptin levels during the night compared with the rise in lean individuals [48]. In the WSCS population, circulating leptin levels were higher in women and were positively correlated with BMI [20]. After adjustment for age, sex, and BMI, leptin levels were positively correlated with insulin levels, but negatively correlated with insulin sensitivity and ghrelin levels. Other associations included diastolic blood pressure, smoking, and blood urea nitrogen levels [20].

Ghrelin is a 28-amino acid peptide hormone synthesized by the stomach [49]. It circulates as active and inactive forms. Active ghrelin is acylated and lipophilic, and therefore can cross the blood–brain barrier. Acute administration of small doses of ghrelin, either systemically or directly into the brain, dramatically increases food intake in rats [50,51]. Chronic systemic administration of ghrelin to rodents results in weight gain and increased fat mass. In addition, ghrelin appears to have an effect on energy expenditure. Calorimetry has suggested that administration of ghrelin causes an increase in respiratory quotient in rodents, but ghrelin negatively correlated with energy expenditure in humans [52]. Several lines of evidence suggest that the primary site of action of stomach-derived ghrelin is within the hypothalamus, an important brain region in the regulation of appetite, energy expenditure, temperature regulation, control of pituitary hormone secretion, water balance, reproduction, and physiological responses to emotional stimuli. Compared with the stomach (where ghrelin-synthesizing cells have been identified as X/A-like cells in the oxyntic glands), much smaller quantities of ghrelin have been observed in the hypothalamic arcuate nucleus and other brain regions [49]. Most current evidence regarding ghrelin's biology stems from studies of its actions as a hormone; however, the individual roles of central and peripheral ghrelin in the regulation of food intake and energy expenditure remain to be determined.

Plasma ghrelin appears to be pulsatile (ultradian secretion) and displays a diurnal rhythm with highest levels at night during sleep [48]. The nocturnal peak in ghrelin is diminished in obese individuals. During the day, plasma ghrelin levels rise before meals, while systemic ghrelin infusion results in hunger [51,53,54]. Ghrelin is therefore believed to be the "hunger hormone". Ghrelin levels are lower after partial gastrectomy, explaining to some extent the success of this procedure in reducing appetite and promoting weight loss. Subjects with Prader–Willi syndrome, which is associated with voracious appetite, have elevated ghrelin levels [55]. In view of the actions of exogenous ghrelin described above, it is likely that changes in endogenous ghrelin represent an adaptive response to fasting, promoting food intake and favoring fat deposition. In the WSCS study, circulating total ghrelin levels were higher in women and negatively correlated with BMI. After adjustment for age, sex, and BMI, ghrelin was negatively correlated with leptin but positively correlated with adiponectin levels (adiponectin is adipocyte-derived and its levels are negatively correlated with fat mass and positively correlated with insulin sensitivity) and insulin sensitivity [20]. Other associations that were found with ghrelin levels included high-density lipoprotein (HDL) cholesterol, creatinine levels, and alcohol intake [20].

In the WSCS population, significant associations were found between serum ghrelin and leptin levels and sleep duration that were independent of age, sex, and BMI (Table 2) [20]. Short sleep duration was associated with low leptin (with a predicted reduction in leptin of 15.5% for habitual sleep of 5 h vs. 8 h), and high ghrelin (with a predicted increase in ghrelin of 14.9% for nocturnal/polysomnographic sleep of 5 h vs. 8 h), independent of BMI [20]. These relationships remained following correction for multiple possible confounding factors including age, sex, BMI, morningness–eveningness tendencies, self-reported exercise, and sleep-disordered breathing [20,56]. These hormone changes are usually observed in reaction to food restriction and weight loss, and are typically associated with increased appetite. The hormone changes observed with sleep duration require comparison with changes after calorie restriction, and similar changes in leptin to those observed with sleep loss have been reported with both acute and long-term calorie deficits [46]. For example, in a study of 50 overweight and obese female volunteers (aged 18–50 years; BMI 25–32 kg/m^2; who were put on a calorie-restricted diet over 3 weeks, the women lost approximately 3.9% of their BMI (p<0.001) and this was associated with a 13.6% increase in levels of ghrelin (p<0.01) [unpublished data from Taheri, University of Bristol, Bristol, UK]. Therefore, high circulating ghrelin and low circulating leptin provide powerful signals to the hypothalamus to promote food intake (Fig. 2). The fact that gastric bypass surgery is associated with low ghrelin levels suggests that lowering ghrelin levels by ensuring adequate sleep may have a significant effect on weight loss.

Recently, data from human laboratory studies using the partial sleep restriction paradigm have suggested that sleep

Table 2. Relationships between sleep variables and ghrelin and leptin, adjusted for age, sex, body mass index, and time of sample storage (adapted from [20]). Leptin and ghrelin levels were square-root transformed. Ghrelin, which is an important short-term regulator of food intake, was found to be associated with polysomnographic (short-term) sleep measures. Leptin, a long-term regulator of food intake, was correlated with measures of long-term sleep (from questionnaire and sleep diary).

Method	Sleep variable	Ghrelin			Leptin		
		n	coefficient	p value	n	coefficient	p value
Polysomnography	Sleep efficiency (proportion)	856	−5.1	0.05	1017	0.15	0.62
	Wake after sleep onset (h)	856	0.81	0.05	1017	−0.041	0.40
	Total sleep time (h)	856	−0.69	0.008	1017	0.047	0.13
Diary	Average nightly sleep (h)	617	−0.52	0.13	709	0.12	0.006
Questionnaire	Usual sleep (h)	855	−0.096	0.72	1015	0.089	0.006

restriction is associated with changes in metabolic hormones (cortisol, growth hormone, insulin, leptin, and ghrelin), increased appetite, and an increased desire for high carbohydrate food [57,58]. This laboratory work suggests that as little as 2–3 nights of sleep restriction can have profound effects on metabolic hormones and appetite [58]. In addition, laboratory studies have suggested a reduction in insulin sensitivity with sleep restriction and, interestingly, it has recently been argued that insulin resistance may actually have a role in the development of obesity [60]. One problem with the available laboratory studies is the use of different sleep restriction paradigms; this is to be expected as this is a novel area of investigation and will be clarified with the increasing research into this topic.

It is clear that data from large population and laboratory studies point to a novel physiological interaction between sleep and metabolism. However, leptin and ghrelin are unlikely to be the only hormones involved. Other metabolic hormones such as peptide tyrosine tyrosine (PYY) [61,62] and hormones whose secretion is associated with sleep and circadian rhythms (e.g. cortisol) are known to have profound effects on appetite and/or body composition and may be affected by changes in sleep duration or quality. Furthermore, changes in these hormones may augment the adverse metabolic consequences of obesity, including insulin resistance and diabetes. To fully understand the physiological interaction between sleep and metabolism, additional human studies are essential, especially studies that investigate individuals with varying sleep durations. These studies will complement studies investigating experimental sleep deprivation in individuals of average sleep duration. Unfortunately, there are few animal models of human sleep. Rodents, which are commonly used to study obesity, do not have consolidated sleep like humans.

Sleep duration and energy expenditure

Sleep deprivation has long been used as a method to gain insights into the biological significance of sleep. While short-term non-pharmacological sleep deprivation is feasible in humans, because of ethical reasons, long-term total sleep deprivation (TSD) has only been performed on experimental animals. Studies in rats using the "disk-over-water" method have provided important insights into the impact of sleep deprivation on health (Fig. 3) [63–66]. It should be noted that in these studies the yoked control also experienced an element of sleep deprivation. The TSD rats died 11–32 days after beginning deprivation having consistently displayed several abnormalities: extreme debilitated appearance, edema of paws, skin lesions, motor weakness, ataxia, and an inability to generate high electroencephalograph amplitude. Interestingly, TSD also resulted in increased food intake but greater energy expenditure, ultimately leading to weight loss. During the late stages of sleep deprivation, the TSD rats had reduced body temperature, reduced plasma thyroxine, and increased plasma norepinephrine.

Changes in energy balance occur early in the TSD model; within a few days of the initiation of TSD, rats exhibit an increase in waking body temperature and, consequently, energy expenditure. TSD rats increase food consumption to compensate for this, yet they lose weight, indicating a dramatic increase in energy expenditure. During the latter part of TSD when death is imminent, energy expenditure increases in conjunction with declining body temperature, suggesting massive heat loss. Interestingly, the deleterious effects of sleep deprivation can be postponed by a high-calorie diet. Therefore, increased food intake is thought to be an adaptive response to the increased energy expenditure during TSD, but the degree to which increased food intake can counteract the increase in energy expenditure is limited, since survival time in these studies was predicted by the rate

Figure 3. The disk-over-water method of sleep deprivation in the rat. When the totally sleep deprived (TSD) rat goes to sleep, this activates the computer to turn the motor and if the TSD rat does not awaken, it lands in the water surrounding the disk. The control rat is also sleep-deprived but gets an opportunity to sleep when the TSD rat is awake. This technique highlighted a potential association between sleep and metabolism. This model is, however, inadequate for studying the mechanisms for the interaction between human sleep and metabolism. Compare this with the human situation where sleep is consolidated, environmental temperature is regulated, and there is free access to high-calorie food.
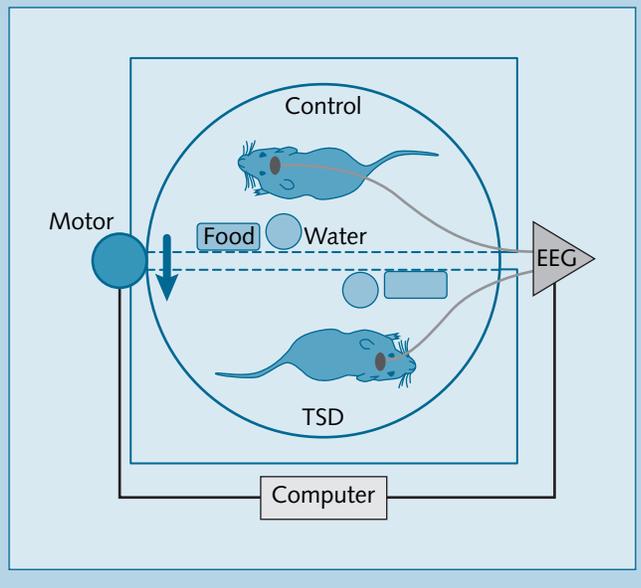
of energy expenditure increase early in deprivation. These results indicate a critical role for sleep in maintaining the ability to thermoregulate during both sleep and wake states. This link is given further credence by the fact that both phylogenetically small mammals and juveniles, which have less thermal stability and thus face greater thermoregulatory challenges, generally sleep more than larger (and older) mammals [67].

It is difficult to reproduce the effects of partial chronic sleep loss as seen in humans in rodent models, which do not have consolidated sleep. Furthermore, it is difficult to have ideal control animals for such experiments. Nevertheless, the disk-over-water method and other approaches have been used to study the impact of sleep deprivation on metabolic hormones. Hormonal studies with sleep deprivation models in rodents have, however, shown conflicting changes in leptin, ghrelin, and corticosterone.

Does sleep deprivation alter the energy balance in humans? To answer this, total and partial sleep deprivation studies have been carried out [57,58,68]. It is difficult to bring about sufficient days of TSD in humans to observe similar effects on energy expenditure as observed in the TSD rat model. However, the loss of a single night of sleep in humans does not typically result in an increase in mean core body temperature. Humans normally experience a drop in core body temperature at night, half of which is due to sleep, the other half of which is circadian. Therefore, the loss of sleep at night results in an inability to lose the resultant excess heat. Failure of thermoregulation and a disruption of sleep in humans have been observed in quadriplegics who lack an ability to actively thermoregulate (this disruption was beyond that caused by sleep apnea in these subjects) [69]. Other changes that have been observed during short-term TSD include an increase in sympathetic nervous system activity, a decreased ability to curtail heat loss in a cool environment [70], and an increase in hunger, which may reflect an increased energy need or a mismatch between energy need and food-seeking behavior. Collectively, these results indicate that short-term TSD is likely to cause a disruption in thermoregulation and energy balance in humans. However, the effects of prolonged partial changes in sleep duration are unknown. The major components of energy expenditure are resting (basal) metabolic rate, thermogenic effect of ingested food, and activity-related energy expenditure (exercise and non-exercise activity thermogenesis [NEAT]). The most variable component is activity-related energy expenditure; it is likely that sleep has an impact on this component as it results in fatigue, but this needs to be confirmed by future studies.

The hypothalamic hypocretin (orexin) system

The lateral hypothalamic hypocretin (orexin) neuropeptide system, known to be abnormal in the sleep disorder narcolepsy, may be key to the interaction between short sleep duration and metabolism [71–73]. Most cases of narcolepsy–cataplexy cases are associated with undetectable hypocretin levels in the cerebrospinal fluid. Post mortem studies have shown absence of hypocretin precursor mRNA expression in brains from patients with narcolepsy–cataplexy. Hypocretin (orexin) neurons are located in the perifornical area and have connections with the hypothalamic arcuate and paraventricular nuclei, important areas for appetite, hormone, and autonomic nervous system regulation. Several studies have reported an association between narcolepsy and excess body weight in the face of reduced appetite [74–77]. Therefore, absent hypocretin (orexin) neurotransmission, as seen in narcolepsy, is believed to result in reduction in energy expenditure, but this requires more careful study. Hypocretin (orexin) neurons are important in the maintenance of wakefulness. They respond to sleep deprivation by activation (Fig. 4) and

Figure 4. The hypocretin (orexin) system may be key to the interaction between sleep and obesity. These neurons are activated by sleep deprivation. **A**: Section from the perifornical hypothalamic region of a control rat stained for hypocretin (grey) and the early transcription factor Fos (black); there are few Fos immunoreactive nuclei. **B**: Section from the perifornical hypothalamic region of an acutely sleep-deprived rat double-stained for hypocretin (orexin) and Fos showing generalized activation of hypocretin (orexin) neurons.
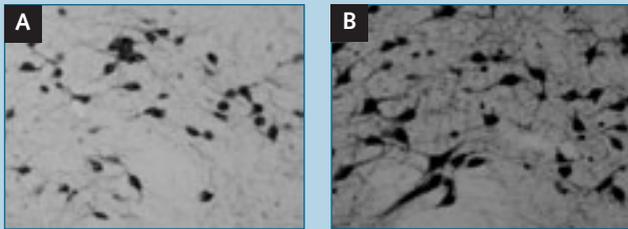
C: Schematic representation of the putative role of hypocretins (orexins) in the sleep deprivation–metabolism interaction and the circuitry involved. Hypocretin (orexin) neurons respond to sleep deprivation and are involved in the regulation of appetite and energy expenditure. They also modulate sympathetic nervous system activity. These neurons respond to peripheral signals such as hormones (leptin and ghrelin) and metabolites (glucose and lipids). The impact of the hypocretins (orexins) on leptin and ghrelin secretion is unknown, but can presumably occur by alterations in autonomic nervous system activity. Additionally, sleep deprivation may exert effects on leptin and ghrelin secretion through hypocretin (orexin) independent mechanisms. These potential pathways require validation by future studies.
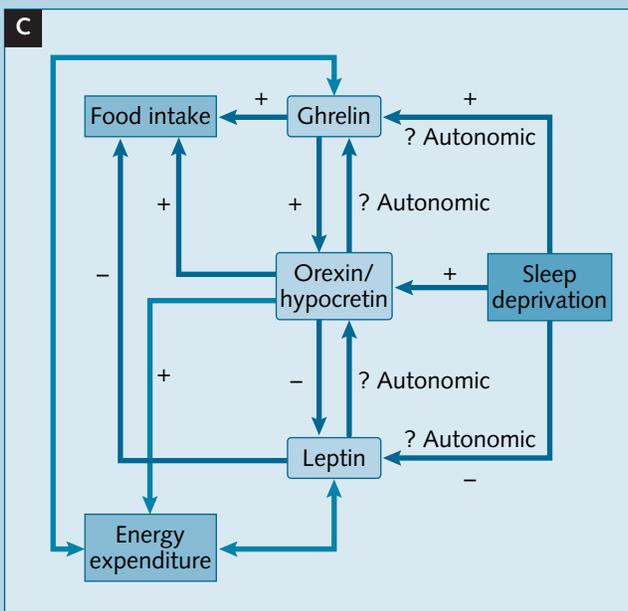
Figure 5. Potential mechanisms through which short sleep duration could result in obesity. Short sleep duration can affect both energy intake and energy expenditure. It results in tiredness that may hamper physical activity, and impairs judgment and alters metabolic hormones to increase appetite and affect food selection. Additionally, extra time awake provides increased opportunity for food intake. Other potential mechanisms include effects of sleep on resting (basal) metabolic rate, thermic effect of food, and non-exercise activity thermogenesis.
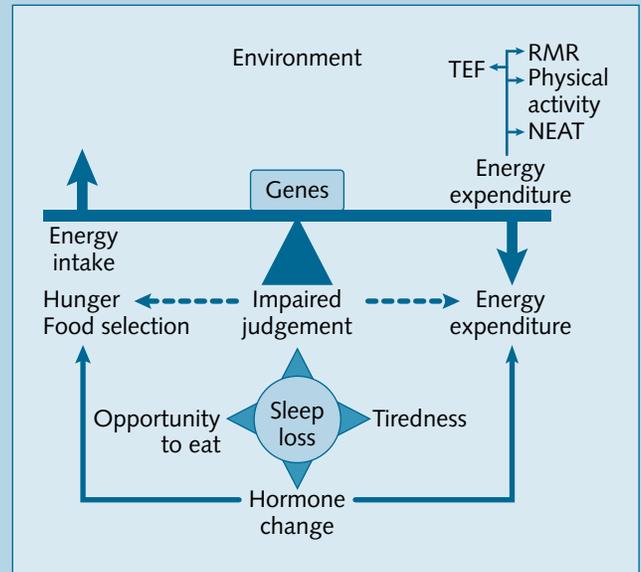
NEAT: non-exercise activity thermogenesis, RMR: resting metabolic rate; TEF: thermogenic effect of food.

are sensitive to peripheral metabolites (glucose and lipids) and metabolic hormones (leptin and ghrelin). Hypocretin (orexin) neurons have been shown to be involved in the regulation of both food intake and energy expenditure, but the effect on the latter may be more important. Furthermore, there may be reciprocal connections between these neurons and peripheral hormones through alterations in sympathetic nervous system activity. Unfortunately, the hypocretin peptides can only be reliably measured in cerebrospinal fluid, making studies in humans difficult. Moreover, it would be difficult to image these neurons since they are few in number and located in a small part of the brain.

Potential mechanisms and research agenda

Figure 5 summarizes the potential mechanisms for the sleep–metabolism interaction. These mechanisms need to be clarified by well-designed population and laboratory studies. Since this interaction is complex, it is likely that multiple interrelated factors operate downstream of sleep duration

and that these combine to result in the observed phenotype (obesity). Sleep duration may alter the balance between energy intake and energy expenditure by affecting both sides of the equation. To investigate this further, we need to answer several fundamental questions. TSD in rats results in increased energy expenditure, but the effect in humans remains to be determined. Could chronic sleep loss also result in increased energy expenditure in humans, and if so, which components of energy expenditure are altered [78]? Sleep loss results in fatigue and excessive daytime sleepiness. Could this fatigue contribute to reduced daytime physical activity? Sleep loss results in alterations in several hormones including leptin, ghrelin, insulin, and cortisol. Could these hormonal changes contribute to selection of calorie-dense food, excessive food intake, alterations in energy expenditure, and insulin resistance? What other hormones/cytokines are involved (e.g. PYY, adiponectin, resistin, visfatin, interleukin-6 [79], and tumor necrosis factor-α)? How does sleep loss translate into all the above changes? Is it through alterations in sympatheto-vagal balance?

Conclusion

There is now sufficient population data to suggest an important association between short sleep duration and obesity. Several potential mechanisms for this relationship have been proposed above and these need to be investigated methodically. Despite our incomplete understanding of the mechanisms and neural circuitry involved, we have to examine the public health implications of our current knowledge. Voluntary sleep restriction is not likely to be the only cause of the current obesity pandemic and it is too simplistic to expect obese individuals to lose weight simply by sleeping more. It may prove difficult to unequivocally prove a causal relationship between short sleep duration and obesity as we are dealing with highly complex physiological systems and current animal models are inadequate. Additionally, it may be difficult to extend sleep for prolonged periods, as is reflected by the scarcity of publications in this area. Intervention studies using sleep extension for weight loss cannot be placebo controlled or blinded, and once obesity occurs the situation is compounded by the occurrence of sleep-disordered breathing [56]. Furthermore, the optimal sleep duration is unclear [80]. It has been argued that the impact of sleep on body weight is likely to be more important in the prevention of obesity in children [21]. We know that short sleep duration at a young age is associated with later obesity and can ensure that parents are educated regarding the importance of sleep so that their children can be provided with the appropriate opportunity and environment for adequate sleep. Good sleep could, for example, be promoted by removal of gadget distractions such as televisions and computers from bedrooms and restricting their use, observance of strict bedtimes, and other sleep hygiene measures [21]. There is little risk in including advice regarding adequate sleep as part of other lifestyle approaches such as healthy eating and physical activity, and any opportunity to halt and reverse the obesity pandemic should be not be lost.

Disclosures

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A Clinical Sleep Laboratory

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What is a sleep laboratory?

William Dement (Stanford Sleep Medicine Center, Stanford University, Palo Alto, CA, USA) established the first formal clinical sleep medicine center at Stanford University in 1972. Since then, there has been a tremendous growth in the number of sleep laboratories where a clinical "sleep study" or polysomnography (PSG) can be performed for the diagnosis and treatment of sleep disorders [1]. However, it was not until the early 1990s that clinical sleep recording could be performed electronically and access to PSG became more widely available [2], and by 2004, it was estimated that the number of sleep studies performed in western countries ranged from 42.5 studies/year/100 000 persons in the UK to 427 studies/year/100 000 persons in the US [3].

Which patients should be referred to a sleep laboratory?

Individuals with suspected sleep-disordered breathing (SDB), complaints of disturbed sleep, abnormal sleep behavior, or severe daytime sleepiness should be referred to the sleep laboratory for a diagnostic PSG [4]. PSG is not routinely indicated to diagnose insomnia, restless legs syndrome (RLS), or circadian rhythm sleep disorders [4]. In addition to diagnosis, therapeutic titration of nasal positive airway pressure (nPAP) for the treatment of SDB is also performed in the sleep laboratory.

A PSG in adults and children is recommended for the diagnosis of the following sleep disorders:

- Obstructive sleep apnea (OSA) should be suspected in those who with loud habitual snoring, obesity, craniofacial abnormalities, daytime sleepiness, and reported apneas. Due to a greater risk of poor health outcomes, it is particularly important to screen individuals with comorbid hypertension, coronary artery disease, atrial fibrillation, stroke, diabetes, metabolic syndrome, or cognitive impairment [5].

- Central sleep apnea (CSA) should be considered in patients with congestive heart failure (CHF), especially those with atrial fibrillation, as CSA may negatively impact cardiovascular outcomes [6].
- Parasomnias such as sleep walking, nocturnal eating disorder, or rapid eye movement (REM) behavior disorder should be considered in patients who report complex motor or violent behaviors during sleep. PSG may be especially useful if injurious behavior has been reported or if nocturnal seizure is suspected. Clinical suspicion of nocturnal movement disorder should be evaluated with PSG. Periodic limb movement disorder is the most common and may be suspected because of complaint of repetitive limb movements during sleep, frequent awakenings, fragmented sleep, difficulty maintaining sleep, or excessive daytime sleepiness.
- Hypersomnias such as narcolepsy should be considered when complaints of excessive sleepiness, sleep attacks, unrefreshing sleep, hypnogagic hallucinations, cataplexy, or sleep paralysis are present. A nocturnal PSG, followed by a multiple sleep latency test (MSLT) or a maintenance of wakefulness test (MWT) is usually required to investigate disorders of hypersomnia.

What types of studies are available in the sleep laboratory?

Sleep laboratories have standard protocols that can be utilized in specific clinical situations (Table 1). Diagnostic PSG and titration studies are conducted during usual sleep time to evaluate and treat sleep-related pathology. Daytime tests (MSLT and MWT) are utilized to quantify sleepiness and evaluate disorders of hypersomnia. A diagnostic PSG is observational only and no intervention is attempted by the polysomnographic technologist (PSGT). The goal is to obtain a snapshot of a usual night of sleep, and assist in making an initial diagnosis. Repeat diagnostic PSG should be performed to evaluate response to non-PAP therapies for OSA such as surgery, dental appliance, or weight loss [4].

If significant OSA has been diagnosed during a diagnostic PSG, and PAP therapy is appropriate, a second full night attended recording, known as a titration study, is performed.

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Table 1. Study protocols offered by sleep laboratories.

Diagnostic PSG

Nocturnal observational study

Performed to diagnose sleep disorders

Used to investigate the success of interventions such as weight loss, ENT, or dental therapy for SDB

Titration study

Night-time study for therapeutic intervention/nPAP introduced

Performed to establish efficacious settings for nPAP

Repeated after weight gain, cardiac events, or if sleepiness persists

Split night study

In the setting of moderate to severe SDB, both diagnoses and nPAP titration are performed in one-night recording

Multiple Sleep Latency Test/Maintenance of Wakefulness Test

A series of nap opportunities performed in the daytime to quantify daytime sleepiness and help to diagnose narcolepsy

ENT: ear, nose and throat; nPAP: nasal positive airway pressure; PSG: polysomnography; SDB: sleep-disordered breathing.

During the titration study, a PSGT will adjust the air pressure delivered until the upper airway is patent, oxygen saturations have normalized, and snoring has resolved. The technologist may use both continuous and/or bi-level PAP devices, and may add supplemental oxygen when appropriate [7]. Specialty devices such as self-titrating (auto) PAPs, or noninvasive ventilators may also be utilized, especially during titration studies performed for hypoventilation associated with neuromuscular disease or CSA [8,9]. Titration studies should be repeated preoperatively, after significant weight gain, with worsening cardiac condition, or if symptoms of sleepiness return [10].

A split night study is performed to both diagnose and treat OSA during a single night of recording. This type of study is usually limited to patients with moderate to severe OSA. If a clear diagnosis of moderate OSA is made after 2 h of sleep, titration of nasal PAP is started. Although reports are varied, compliance and efficacy of PAP therapy appears equal between split night and full night titrations [10].

The MSLT, to measure sleep onset latency, is performed after a patient awakens from a diagnostic PSG, and consists of five 20-min nap opportunities. Each nap is performed in the dark, 2 h apart; the patient should be instructed to "please lie quietly, assume a comfortable position, keep your eyes closed, and try to fall asleep". During the MSLT a complete PSG set up is not required; however, electroencephalogram (EEG) monitoring with electro-oculography (EOG) is needed

to document sleep onset and rapid eye movement (REM) sleep. The MSLT is useful in quantifying sleepiness due to a sleep disorder and in diagnosing conditions such as narcolepsy or other hypersomnias.

In the MWT, five 40-min monitoring opportunities occur. The patient is instructed to sit still and remain awake for as long as possible, look directly ahead, and not to look directly at the light. Unlike the MSLT, the MWT is not a diagnostic test, but instead estimates an individual ability to stay awake [11]. The MWT test allows a clinician to evaluate the effectiveness of a therapeutic regimen, or assess safety [12,13].

Nocturnal penile tumescence testing (NPT) adds measurements of erectile function to standard diagnostic PSG, as Stage REM sleep is associated with spontaneous erections. Although these studies were more commonly conducted in sleep centers in the past, recent advances in therapeutic options for erectile dysfunction have relegated these studies to only infrequent use in medical practice [14].

What type of information is obtained in the laboratory?

A typical sleep study requires the monitoring of multiple physiological signals including EEG, chin electromyogram (EMG), EOG, electrocardiogram (ECG), thoracoabdominal movement, oronasal flow, tibial EMG, oxygen saturation, body position, snore monitor, and video recording. Techniques may vary greatly, limited channel and unmonitored PSG are active areas of investigation [15].

In 1968, a standard was agreed that allowed for unified interpretation of sleep stages, meaning that sleep could be analyzed as progressing through several recognizable stages throughout the night (Fig. 1). An updated scoring manual that includes rules for scoring sleep stages as well as for scoring arousals, respiratory events during sleep, movements during sleep and cardiac events will be available in 2007 [16].

Sleep-related breathing disorders are quantified by interpretation of the data from thoracoabdominal effort monitors, oronasal flow signal, and pulse oximetry. Breathing pauses lasting ≥10 s are characterized as either central (without thoracoabdominal effort) or obstructive (thoracoabdominal effort noted). Air flow may be reduced (hypopnea) or absent (apnea). Oxygen desaturation and arousals and brief awakenings during sleep, identified by EEG, support a diagnosis of sleep apnea (Fig. 2) [17].

Tibial EMG is used to quantify the frequency of periodic leg movements during wake and sleep. A series of ≥4 events, with each event lasting 0.5–5.0 s, and an intermovement interval of 4–90 s, is defined as a group of periodic limb movements (Fig. 3) [18,19].

In addition to EEG, EOG, EMG, and respiratory measures, several other parameters may be monitored. For example,
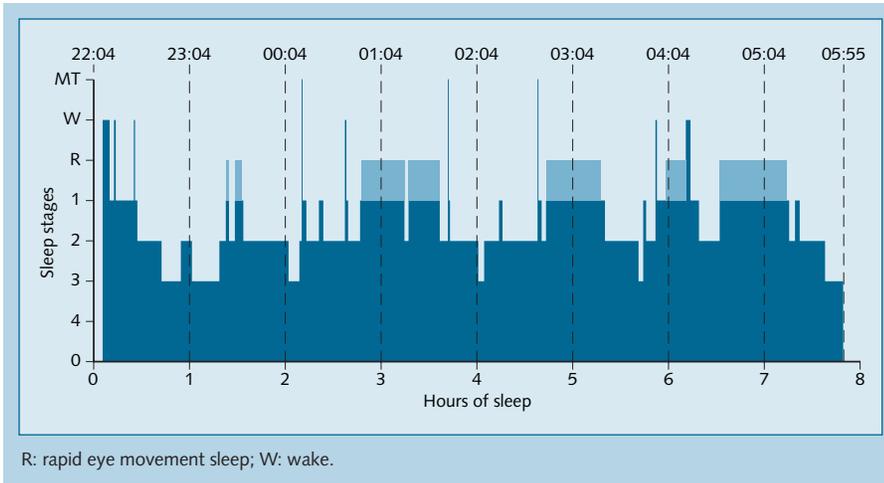
Figure 1. An example of a normal night of sleep. Sleep stages are displayed on the y axis and the number of hours of recording on the x axis. Slow-wave sleep occurs during stage 3 and 4 sleep. Note that there are five cycles of sleep throughout the recording with slow wave predominating in the first half of the night and rapid eye movement sleep predominating in the second half of the night.

R: rapid eye movement sleep; W: wake.
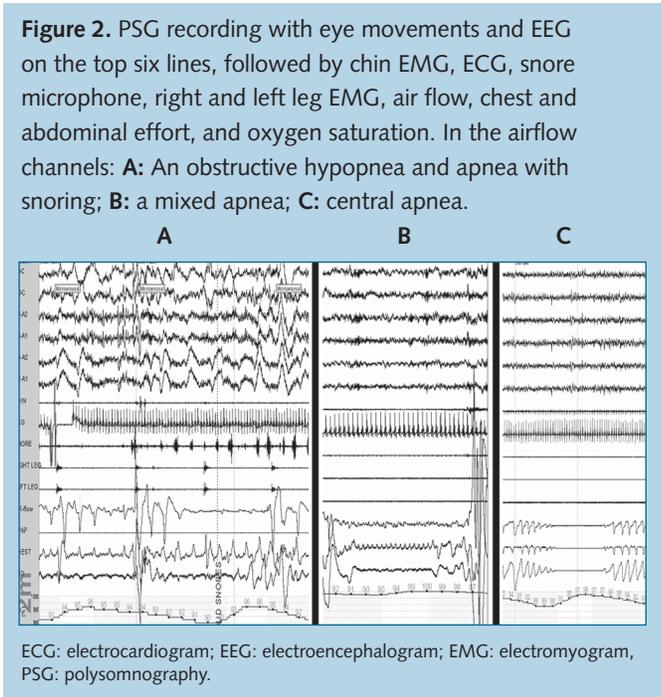
Figure 2. PSG recording with eye movements and EEG on the top six lines, followed by chin EMG, ECG, snore microphone, right and left leg EMG, air flow, chest and abdominal effort, and oxygen saturation. In the airflow channels: **A:** An obstructive hypopnea and apnea with snoring; **B:** a mixed apnea; **C:** central apnea.

ECG: electrocardiogram; EEG: electroencephalogram; EMG: electromyogram, PSG: polysomnography.

Figure 3. A 2-min standard PSG recording showing periodic limb movements of sleep. Eye movements and EEG on the top six lines, followed by chin EMG, ECG, snore microphone, left leg EMG, air flow, chest and abdominal effort, and oxygen saturation.

ECG: electrocardiogram; EEG: electroencephalogram; EMG: electromyogram, PSG: polysomnography.

video recording is particularly useful in patients with suspected seizure or parasomnia; increased chin EMG activity, such as bursts of tonic activity, may indicate tooth grinding or bruxism [19,20]; the ECG tracing may reveal arrhythmias either in relation to OSA or sleep stage. [21].

Patient preparation for PSG

Preparing a patient for PSG can help to ease anxiety and improve the patient's experience (Table 2) [22]. Defining the goals of the study ahead of time can be helpful; patients should know the type of investigation they are being sent for and the reason the study is being performed. Patients should understand the devices needed for monitoring, and the time commitment. The patient should be in their usual state of health, and should avoid radical changes from their

usual sleep habits. The use of transitional objects or rituals is welcome in the sleep laboratory and bringing a favorite pillow, a book to read, or a hot drink may be helpful [23]. Alcohol or medications such as sleep aids should not be abruptly halted or added just for the purpose of recording sleep. As nasal obstruction is a significant risk factor for nPAP intolerance, a strategy to improve nasal congestion and drip should be in place prior to nPAP titration [24].

Patients with special needs

Identifying those patients with special needs will help the sleep laboratory to better prepare for an individual's study. The sleep laboratory should be informed ahead of time if the patient requires wheelchair accessibility or language translators. Morbidly obese patients may benefit from a larger mattress while those who are unable to transfer to the bed may need an assisted lift device. Home healthcare aides should be present for a PSG if the patient requires care during the night. Those with severe or complicated active medical

Table 2. Preparing a patient for PSG.

Record a 1-week sleep diary
Choose the correct protocol
Diagnostic PSG
Split-night study
PAP titration study
MSLT/MWT
Stay in usual sleep routine
Study to begin at the habitual sleep time
No sleep medication changes
Bring comfortable items from home such as pillows, music, and sleep attire
Returning PAP titration patients should bring their comfortable home mask interface
Test should be performed in a usual state of health
Large meals or excessive alcohol should be avoided before the test

MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; PAP: positive airway pressure; PSG: polysomnography.

Table 3. Important data that can be obtained from polysomnography and the normal and abnormal values [28,29].

	Normal	Abnormal
Sleep onset latency	10–20 mins	≤8 mins
Wake time after sleep onset	<9% of the recording	>15% of the recording
Periodic limb movement index	0	>5/h
Apnea–hypopnea index	0–5 events/h	Mild: 5–15 events/h Moderate: 15–30 events/h Severe: >30 events/h
Mean MSLT	> 10 mins	≤8 mins.
SO REM	None	≥2

MSLT: mean sleep latency test; SO REM: sleep-onset rapid eye movement.

conditions may be better served by a hospital-based rather than a stand-alone laboratory.

When children are studied in the sleep laboratory some adjustments are made. Parents may be asked to accompany their children and stay with them during the study. Unlike adults, children may develop obstructive hypoventilation rather than discrete obstructive events, therefore expiratory end-tidal CO_2 may be monitored from a nasal cannula in order to measure hypoventilation. Transcutaneous CO_2 monitoring can be used for children who do not tolerate a nasal cannula [25].

The sleep laboratory schedule

The sleep laboratory visit begins with patient education about the types of sleep disorders and the health impacts of these conditions. Before a titration study, the use and care of nPAP devices should be reviewed and mask fittings with several mask types prior to titration is key since mask problems significantly impact on overall compliance [7]. The monitoring leads are placed on the patient, and the study begins. The patient should be aware that the PSGT will need to enter the room to adjust the monitoring devices throughout the night. Although supine REM sleep is a prominent time for the development of SDB, patients are free to sleep in any position [26]. The overnight study ends at the patient's usual awakening time [12,13].

How to interpret the PSG Report?

The data included in a PSG report can be extensive; therefore, focusing on a few numbers may help to distill the findings to the crucial elements (Table 3). A complete PSG should demonstrate all stages of sleep and have at least 120 min of

total sleep time. If the periodic limb movement index (PLMI) or the number of limb movements per hour of sleep is >5, clinical evaluation should be performed to asses the possibility of RLS [19].

The apnea–hypopnea index (AHI) or respiratory disturbance index (RDI) represents the number of respiratory events per hour of sleep. These events help to asses a patient's risk of hypertension and estimate the severity of SDB. In general, the AHI is normal from 0–5 events/h, mild from 5–15 events/h, moderate from 15–30 events/h, and severe when greater the 30 events/h [27]. Other key findings include the oxygen saturation nadir, heart rate, and arousal index. Oxygen desaturation out of proportion to the degree of SDB may suggest an underlying cardiopulmonary deficit. When an MSLT is performed for the evaluation of excessive sleepiness, an average sleep latency of ≤8 min is consistent with hypersomnia. Together with patient history, the presence of REM sleep during naps is consistent with narcolepsy.

If the patient's complaints are not explained by the results of the sleep study, other causes of sleep disturbances, such as increased upper airway resistance, gastroesophageal reflux, or insomnia, may be considered, and the patient should be referred to a sleep specialist for further investigations.

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CLINICAL REVIEWS
Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Christopher Drake, Andrew Krystal, Pedram Navab, Adam Spira, and Birgit Wiswe

SLEEP APNEA

The link between obstructive sleep apnea and heart failure: underappreciated opportunity for treatment
Naughton MT.
Curr Heart Fail Rep 2006;**3**:183–8.

Evidence from epidemiological and animal studies suggests a causal association between obstructive sleep apnea (OSA) and poor cardiovascular outcomes, including congestive heart failure (CHF). The author describes continuous positive airway pressure as a promising treatment for both OSA and CHF.

Systemic hypertension and ischemic heart disease (IHD) are potential causes of congestive heart failure (CHF), and are both associated with obstructive sleep apnea (OSA). The author of this review reports that animal studies and human epidemiological research suggest a causal association between OSA and systemic hypertension, and that treatment of OSA by continuous positive airway pressure (CPAP) has been shown to reduce blood pressure. He further explains that OSA causes damage to the endothelium, potentially leading to generalized atherosclerosis and, eventually, IHD. Evidence for a causal link between OSA and IHD is presented. This includes a high prevalence of OSA in myocardial infarction survivors, and an increased risk of cardiovascular disease and mortality among individuals with OSA.

Dr Naughton estimates that 30% and 35% of patients with systolic and diastolic CHF, respectively, have OSA, and that 30% of patients with CHF suffer central sleep apnea. Evidence for a link between OSA and CHF is presented, including epidemiological findings of a strong association between OSA and CHF, and reports of low left ventricular ejection fraction (LVEF) in 8–62% of OSA patients.

In addition, the author reports that treatment with CPAP improved LVEF in several clinical trials of patients with CHF, and that there is some evidence that CPAP reduces LV chamber size and blood pressure, and improves quality-of-life

measures in these patients. Furthermore, several studies have indicated that CPAP might reduce mortality rates in patients with OSA, and perhaps even in CHF patients with OSA. The author reports that CPAP likely reverses the negative cumulative effects of OSA and improves cardiac function by increasing intrathoracic pressure, thereby leading to a series of cardiovascular changes, and improving lung volume. Patient follow-up is critical to address any discomforts (e.g. poor fitting mask, inadequate humidification) and promote adherence to CPAP therapy, which, in general, is poor.

Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients
Sergi M, Salerno DE, Rizzi M et al.
J Glaucoma 2007;**16**:42–6.

Patients diagnosed with obstructive sleep apnea have a higher prevalence of normal tension glaucoma. The relationships that exist between these two conditions were further examined by the authors of this study.

Along with the known higher prevalence of normal tension glaucoma (NTG) in women and the elderly, several vascular diseases have been shown to play a role in the development of this disorder. Some of the vascular diseases associated with NTG have also been demonstrated to be a consequence of obstructive sleep apnea (OSA). Therefore, the authors of the current study analyzed the prevalence of NTG in OSA patients and OSA as a risk factor for NTG.

A total of 91 subjects participated in this study, 51 with OSA and 40 controls. Each individual underwent two nights of polysomnography and received a complete ophthalmological examination prior to OSA treatment.

Of the 51 OSA patients, three were diagnosed with NTG; none of the control group was found to suffer from this disorder. Ophthalmological examination revealed several

significant differences between the OSA group and controls, including an increased thickness in the retinal nerve fiber layer in OSA patients, increased visually evoked potential and pattern electroretinography latency, and reduced amplitude.

The results of this study further enhance the growing information about OSA and its comorbidities. In addition, when considering the severe effects of NTG on individuals, early identifiers for its development risk are essential. Proper treatment of OSA may impact the risk of NTG in certain individuals; however, further research is needed to develop a greater understanding of the relationship of OSA severity and treatment with NTG.

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The effect of altitude descent on obstructive sleep apnea

Patz DS, Spoon M, Corbin R et al.
Chest 2006;**130**:1744–50.

This practical study investigated the effects of altitude descent in the detection of sleep-disordered breathing events, as recorded by polysomnography. Eleven patients from Colorado who were previously undiagnosed with obstructive sleep apnea (OSA) underwent diagnostic polysomnographies at their residential altitude (>2400 m) and at 1370 m, while five participants were also studied at sea level. The mean apnea–hypopnea index (AHI) fell significantly with the initial descent (p=0.022), and in the five patients who travelled to sea level there was a corresponding further decrease. A reduction in the hypopneas and central apneas, but a lengthening in the duration of the obstructive events, was observed with descent using the AHI. The authors surmise that a polysomnogram performed on patients at a lower altitude than where they are currently residing will underestimate both the detection and degree of OSA.

The implications of spatial elevation with regard to atmospheric changes need to be addressed in those with potential sleep-disordered breathing, such as in obstructive sleep apnea (OSA), as oxygen content and barometric pressure are consequently altered and, hence, may lead to a "polysomnographic misreading" of the breathing events. The authors of this study used this concept as a basis on which to pose the practical dilemmas of a patient with symptoms of OSA who requires a polysomnogram that is potentially only available at an elevation lower than his or her residence. What would be the consequences of such a

descent on a diagnosis of OSA as well as on the type of apnea present?

The study involved eleven participants with suspected OSA who resided at an altitude >2400 m in Colorado, USA. Subjects underwent two diagnostic polysomnograms, one at their residential elevation and the other at 1370 m. Five of the eleven patients also underwent a third polysomnogram, performed at sea level. Patients were aged 46–70 years with a body mass index of 20–58 kg/m^2. Results of the study revealed significant improvements in the apnea–hypopnea index (AHI) with each altitudinal descent: an AHI of 49.1±10.5 events/h at residential elevations, 37.0±11.2 events/h at 1370 m, and 33.1±12.6 events/h at sea level. However, the patients with the most severe OSA showed least improvements with regard to their AHI, showing only an average 7.2 events/h decrease. Central apneas decreased by 70% (p=0.06) and hypopneas decreased by 49% (p=0.008) with the altitudinal descents. Obstructive and mixed apneas did not show a similar reduction and, in fact, the duration of these events was longer at the lower elevations. As expected, average non-rapid eye movement arterial O_2 saturation rose correspondingly with the altitudinal descents.

It must be emphasized that although the AHIs revealed a significant reduction with altitudinal descent, the frequency and duration of obstructive apneas actually increased. The authors surmise that at higher elevations, the falling O_2 and rising PCO_2 levels provide a stronger stimulus in triggering an arousal, which may shorten the frequency and duration of the obstructive apneas. In summary, the results of the study revealed significant reductions in the AHI with altitudinal descent that should be strongly considered when ordering a diagnostic polysomnogram for a patient living at higher elevations.

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Putting sleep apnea to rest: tailored therapy reduces fatigue-related risks

Alvi A, Lee SE.
Postgraduate Med 2006;**119**:46–53.

Sleep apnea is a common disorder, and is comprised of two subtypes, obstructive sleep apnea and central sleep apnea. This article provides recommendations for the assessment and treatment of these conditions. Continuous positive airway pressure therapy is discussed, and suggestions to promote adherence are given.

Sleep apnea is a common disturbance, with acute consequences of sleep fragmentation and daytime sleepiness. Apnea is associated with increased risks of poor cardiovascular

outcomes and mortality. In the present article, Alvi and Lee define various sleep apnea syndromes, and describe issues related to diagnosis and treatment.

Two important apnea subtypes are obstructive sleep apnea (OSA) and central sleep apnea (CSA). In OSA – the more common subtype – apneas and hypopneas are due to airway obstruction, often producing airway narrowing and snoring. Risk factors include obesity, male sex, greater neck circumference, and craniofacial abnormalities. In CSA, central nervous system damage or dysfunction produces instability in respiration.

The authors recommend that patients in whom sleep apnea is suspected should undergo a physical examination for risk factors and the affected individual, and, if possible, their bed partner should be interviewed to provide a thorough sleep history. Polysomnography is then required to confirm a diagnosis of sleep apnea and to determine its severity. Patients with moderate-to-severe apnea, i.e. those with an apnea–hypopnea index >5, and excessive daytime sleepiness or a history of congestive heart failure or stroke may benefit from treatment.

Continuous positive airway pressure (CPAP) therapy has been identified as the first line of treatment for OSA; however, adherence to CPAP is often problematic due to nasal discomfort, claustrophobic responses, ill-fitting masks, and an intolerance of the air pressure used. Supportive follow-up, nasal corticosteroid sprays, heating and humidification of air, adjustment of the mask to prevent leaks, alternation of mask types (e.g. nasal pillows or full face mask), and adjustment of air pressure can help reduce discomfort. Other non-surgical interventions for apnea include weight loss, exercise, and oral devices that reposition the mandible or tongue, and are for use in patients with mild OSA who do not adhere to CPAP.

Alvi and Lee suggest that surgical options, such as oropharyngeal or maxillofacial surgery – and in some cases, tracheotomy – be reserved for individuals with OSA and particular craniofacial abnormalities who do not derive a benefit from CPAP treatment or other non-invasive interventions.

Comparison of CPAP titration at home or in the sleep laboratory in the sleep apnea hypopnea syndrome

Cross MD, Vennelle M, Engleman HM et al.
Sleep 2006;**29**:1451–5.

The ability to carrying out polysomnography in a patient's home is an attractive option. This study explored the possibility of home titration of optimal

pressure for the continuous positive airway pressure (CPAP) treatment of obstructive sleep apnea–hypopnea syndrome (OSAHS). The authors found that patients undergoing laboratory and home studies did not differ in CPAP pressure, daytime sleepiness, functionality, or quality-of-life measures. However, the degree to which these findings can be generalized beyond the use of auto-titrating CPAP machines are unclear.

In-laboratory polysomnography (PSG) has long been the gold standard for diagnosis of sleep-related breathing disorders and for titration of continuous positive airway pressure (CPAP) therapy. However, the possibility of carrying out polysomnography in a patient's home would be attractive due to:

- Decreased costs of diagnosing and treating sleep disorders.
- Increased access to medical care for patients with sleep disorders
- Improved information on how patients sleep in the environment where they experience their disorder.

This study by Cross and co-workers assesses the possibility for home titration of the optimal pressure for CPAP treatment for obstructive sleep apnea–hypopnea syndrome (OSAHS). A randomized trial was performed comparing 1-night in-laboratory CPAP titration versus 3 nights of at-home titration in 200 patients with documented OSAS using an auto-titrating CPAP device. Subjects were subsequently prescribed fixed-pressure CPAP treatment based on their titration for on-going therapy. Outcome measures included the identified optimal treatment pressure, two measures of daytime sleepiness: the Epworth Sleepiness Scale score and the Oxford Sleep Resistance Test, and two measures of functionality/quality-of-life: the Short Form-36 and the Functional Outcomes of Sleep Questionnaire.

The authors found that the patients undergoing laboratory and home studies did not differ in CPAP pressure, daytime sleepiness, functionality, or quality-of-life measures. When interpreting these results, it is important to bear in mind that an auto-titrating CPAP machine was used in this study. While there are some data suggesting the comparability of auto-titrating and standard CPAP titration, it remains to be established whether at-home CPAP is comparable to a standard laboratory procedure. Another notable consideration is that this study compared 3 nights of home CPAP titration with 1 night of laboratory CPAP titration, as many subjects lived far from the laboratory and requiring them to make the long drive to the laboratory twice in 24 h was considered undesirable. However, analysis of single-night data from home titration suggests the comparison of one laboratory night with three home nights was not likely to have

confounded the results of this study. Major strengths include the number of subjects, the 3-month follow-up, and the implementation of random assignment.

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Clinical evaluation in predicting childhood obstructive sleep apnea

Xu Z, Cheuk DK, Lee SL.
Chest 2006;**130**:1765–71.

Research determining the factors that are most sensitive and/or specific in predicting childhood obstructive sleep apnea (OSA) has been insufficient. The present study aimed to elucidate whether factors such as symptomatology, patient history, and radiographic findings have a greater predictive value when combined. Retrospective data from 50 children who were assessed on a variety of parameters were analyzed. The most conspicuous and sensitive predictors of OSA in this pediatric population were the combination of upper airway narrowing and mouth breathing or nocturnal enuresis, reaching a sensitivity of 90.3%.

A screening tool to select children who may suffer from obstructive sleep apnea (OSA) is highly desirable given the scarcity and economic limitations of using polysomnography. However, so far, no one factor has shown sufficient sensitivity as a marker for an accurate diagnosis of OSA in children. The researchers of this study retrospectively analyzed data from a cohort of children, aged 4–18 years, to determine whether a combination of factors, including patient history, physical examination, and diagnostic testing, would yield a higher sensitivity and/or positive predictive value.

Each subject underwent a clinical evaluation that included history, physical examination, radiographic assessment of the upper airway, and overnight polysomnography. An apnea–hypopnea index (AHI) >5 was used as a clinical designation of OSA. Based on this criterion, 31 patients were classified as having OSA and 19 as being primary snorers. Although there was a significant difference between the two groups with regard to observed apneas, nocturnal enuresis, and intrusive naps, none had a high sensitivity or specificity in predicting OSA. In terms of the physical examination, moderate-to-severe tonsillar hypertrophy and the presence of mouth breathing, the latter having 100% specificity, differentiated the two groups, albeit with a low sensitivity. The combination of upper airway narrowing and mouth breathing or nocturnal enuresis yielded the highest sensitivity, with a value of 90.3%. Conversely, if the child did not have this combination of factors, there was a 78.6% chance that

OSA was not present. In contrast to adults, the presence of OSA in children does not have associated signifiers, such as obesity, allergic rhinitis, or craniofacial abnormalities.

This study ultimately points to the effectiveness and importance of using a variety of parameters, including parental reporting of intrusive naps and enuresis, as well as the physician's assessment of mouth breathing and upper airway narrowing, that, when combined, lead to a greater sensitivity in predicting the presence of OSA in children. As the authors themselves acknowledge, this study has a number of weaknesses, including the small sample size and the preferential selection of patients with suspected OSA, which limit the applicability of these findings to the general pediatric population. More controversially, the authors utilized an AHI >5 for a clinical designation of OSA compared with other studies that suggest statistical significance at 1 or 1.5, which could have considerably skewed the data and yielded lower specificities and/or higher sensitivities of the factors investigated.

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Clinical characteristics of obstructive sleep apnea in community-dwelling older adults

Endeshaw Y.
J Am Geriatr Soc 2006;**54**:1740–4.

It has been postulated that obstructive sleep apnea (OSA) presents in a clinically distinct manner in elderly adults. This study, in which 30 subjects aged ≥60 years, underwent overnight ambulatory polysomnographies with correlative questionnaires and kept sleep diaries, was designed to test this hypothesis. Of the 94 participants who completed the study, 30 were found to have at least moderate cases of OSA without significant correlations of increased body mass indices, neck circumferences, or snoring. Symptoms and signs that were more conspicuous included a higher Epworth Sleepiness Scale, an increased frequency of nocturia, and unrefreshing sleep. These results show the atypical presentations of OSA in this group.

Although it has been estimated that 20% of those aged ≥60 years suffer from moderate-to-severe obstructive sleep apnea (OSA), it remains under-diagnosed in this cohort. This may be due not only to the group's multiple medical comorbidities and polypharmaceutical effects, but also, as this study argues, due to the atypical presentations of OSA in this population. The traditional risk factors for OSA are typically considered to be snoring and increased body

mass index (BMI) and neck circumference, signs that, as is suggested here, are not well-correlated with its presentation in the elderly.

The participants in this study were community-dwelling, independent adults, aged ≥60 years, who were without significant medical comorbidities and did not have a previous diagnosis of OSA. As the data from this study were gathered from a previous investigation examining the relationship between nocturia and sleep-disordered breathing (SDB), participants were also excluded if they had medical issues secondary to renal abnormalities.

An overnight ambulatory polysomnogram was utilized to determine the presence of SDB, the Epworth Sleepiness Scale (ESS) provided information about the degree of sleepiness, and a self-administered questionnaire was given to all patients to obtain information about sleep patterns. A focused physical examination determined the presence of typical risk factors for OSA, such as neck circumference, BMI, and cardiovascular status.

Of the 94 participants who completed the study, 30 (15 male) were diagnosed with moderate-to-severe OSA without a significant correlation between either the severity of the OSA and BMI or snoring. The mean neck circumference was significantly lower in this cohort diagnosed with OSA compared with the traditionally cited values in the general population of OSA patients. The study also revealed that unrefreshing sleep, higher ESS scores, and an increased frequency of nocturia were significant and independent predictors of OSA in this elderly subject group.

Although there did not appear to be a significant correlation between the presence of snoring and OSA status, it must be recognized that snoring was self-reported and this may not therefore be an adequate reflection of its certainty, especially in those participants who did not live with a partner. Interestingly, the weak association between BMI and SDB in these participants, as the author suggests, could be secondary to anatomical and functional alterations of the upper airway, such as that seen in edentulism, or to age-related decreases in the activity of upper airway musculature, features that are more prominent in the elderly. Unfortunately, and a shortcoming of the study, an upper airway examination was not initially performed in this cohort. This could have made this investigation more robust in its comparison with other traditional risk factors for OSA, namely a narrow airway. Other drawbacks in this otherwise interesting study include a small sample size and the data being derived from another study whose aims and goals were different to that of the present.

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Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy

Tauman R, Gulliver TE, Krishna J et al.
J Pediatr 2006;149:803–8.

The use of adenotonsillectomy is widely accepted as a first-line treatment for obstructive sleep apnea syndrome (OSAS) in children. As previous studies have shown a significant number of postoperative patients with persistent signs of OSAS, the authors of this study attempted to further quantify and qualify this finding. They also assessed the contribution of various risk factors to the surgical outcome by performing pre- and postoperative polysomnographic evaluations. The findings revealed that complete normalization of respiratory parameters occurs in only 25% of surgical patients. Both obesity and a greater initial apnea–hypopnea index were associated with lesser degrees of postoperative sleep normalization.

Obstructive sleep apnea syndrome (OSAS) in children has been associated with a number of significant detrimental health effects that include cardiovascular, behavioral, and growth issues. A number of previous assessments of the efficacy of adenotonsillectomy have shown that this procedure fails to completely correct OSAS in a significant number of patients. Furthermore, these studies were frequently limited by the small number of subjects as well as a lack of complete pre- and postoperative sleep study data.

The study authors used both pre- and postoperative sleep studies, along with a detailed assessment of possible risk factors, to further clarify the efficacy of this treatment. Study subjects underwent a standard adenotonsillectomy performed by one of several surgical teams in the Louisville (KY, USA) area. Two standard nocturnal sleep studies were performed on 110 patients (aged 1–16 years [mean age 6.4±3.9 years], 60% male, 52% obese, 40% with a positive family history of sleep-disordered breathing, and 71% with allergies) and 22 control children. Other data, such as the presence or absence of obesity, positive family history of sleep-disordered breathing, and allergic rhinitis were also gathered. A relative body mass index was calculated for all subjects. An apnea–hypopnea index (AHI) index of ≤1/h total sleep time (TST) was considered to indicate the absence of OSAS. An AHI >1/h but <5/h was classified as mild OSAS, while an AHI >5 determined OSAS. The control group included non-snoring children with an AHI <1/h.

This study reported that adenotonsillectomy does yield significant improvements in sleep parameters, although the results concurred with previous assessments indicating only approximately 25% of the surgical patients achieved complete

resolution of their OSAS. The presence of obesity raised the likelihood of persistent OSAS to 36.4%. Mild OSAS was present in 46% of the patients postoperatively, while 29% still had an AHI >5 postoperatively. There was a greater ratio of hypopneas rather than apneas post-surgically, indicating an overall relative decrease in sleep abnormalities. Children with allergies had a significant higher AHI pre- but not postoperatively. Sleep architecture assessments indicated an improvement after surgery, furthering the assumption that OSAS disrupts normal sleep architecture.

These findings again raise concerns about the efficacy of adenotonsillectomy and emphasize the need for post-operative polysomnography, especially in obese patients. As mentioned by the authors, the lack of oropharyngeal anatomical data and upper airway collapsibility measures prevented assessment of these factors as possible contributors to adenotonsillectomy "failure".

Positional therapy for obstructive sleep apnea patients: A 6-month follow-up study

Oksenberg A, Silverberg D, Offenbach D et al.
Laryngoscope 2006;**116**:1995–2000.

This study investigated whether avoidance of the supine position in patients with primarily positional obstructive sleep apnea (OSA) is symptomatically valuable. Using positional therapy via the tennis ball technique (TBT), a group of 78 patients with positional OSA underwent a 6-month therapeutic trial, and were assessed using polysomnographic and subjective data. Of the 50 respondents to the follow-up questionnaire, 62% (comprised mainly of older patients) stated that they had obtained significant benefits using the TBT with regard to improvements in sleep quality and daytime alacrity, as well as decreased snoring. The remaining 38% were a younger subset of patients who mainly discontinued the TBT due to discomfort.

Although a large number of patients suffer from positional obstructive sleep apnea (OSA), where sleep-disordered breathing events occur mainly in the supine position, little data have been offered to support positional therapy for these patients. The authors of this study aimed to determine whether the tennis ball technique (TBT), where a tennis ball is placed into the pocket of a wide cloth belt and wrapped around the chest so as to lay in the middle of the back, would be a valuable therapy for allaying the subjective complaints of those with positional OSA.

Seventy-eight patients who were consecutively diagnosed with this form of OSA, and who refused continuous positive airway pressure (CPAP) therapy, were enrolled in this 6-month study. The authors postulated that since there is a higher prevalence of positional OSA in mild-to-moderate cases, and as CPAP therapy in patients with mild OSA is less likely to be successful, the TBT would be a particularly apt treatment.

The patients, who underwent polysomnographies, were selected due to the extent of positional effect on their sleep-disordered breathing events, i.e. an apnea–hyponea index (AHI) at least double the lateral. Subjects were further classified into groups by the severity of their OSA: mild, moderate, or severe.

After the treatment phase, 50 patients completed question-naires detailing their compliance with, and symptomatic effects of, the TBT. Of these:

- 38% (Group A) stated that they were continuing the TBT.
- 24% (Group B) replied that they had maintained the lateral position despite discontinuation of treatment.
- 38% (Group C) maintained that they had discontinued treatment after 1 month and had not learned to sleep in a lateral position.

Age was a determining factor in the three groups; Group C tended to be younger patients, as were the group who did not complete the questionnaires. The patients in Group A who were still using the TBT had significant improvements with regard to sleep quality (p<0.005), snoring (p<0.003), and daytime alacrity (p<0.046), compared with the other groups. The principal reason for discontinuation of the TBT was discomfort, although other reasons stated on the questionnaires included detecting no symptomatic improvements, backache, and inefficacy. Interestingly, 12 patients with positional OSA who were not included as initial subjects underwent nocturnal poly-somnographies with the TBT and, although improvements were noted in slow-wave sleep, no changes were seen in total sleep time or sleep efficiency.

This study revealed a positive symptomatic relief in 62% of patients who underwent the TBT as a treatment for their positional OSA. No improvements were reported by 38%, predominantly due to compliance; this group was generally younger. The authors themselves acknowledge several limitations in this study:

- The general outcome of the TBT may be worse than the data analysis suggests as those who did not return the questionnaires could be speculated to have worse outcomes than the responders.

- The data relied on subjective assessments and compliance with the TBT, which could not be verified.
- The absence of a placebo group precluded a randomized, controlled study.

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EPIDEMIOLOGY

Sleep disorders in Parkinson's disease: facts and new perspectives

Manni R, Terzaghi M, Pacchetti C et al.
Neurol Sci 2007;**28**:S1–5.

Sleep problems are common among patients with Parkinson's disease (PD), but are often not diagnosed or treated. This review raises a number of points that are important for both clinical practice and PD research. The authors reiterate how the pathophysiology of PD includes dysfunction of neuronal sleep-related systems and how sleep disorders in this population can emerge from the primary PD pathology, frequent comorbid illnesses, or medications used to treat this condition. The authors underscore the need for adequate diagnosis and treatment of PD, and review key considerations for clinical management.

Sleep problems are estimated to affect 40–90% of patients with Parkinson's Disease (PD) and yet, in 2002, only 40% of neurologists in primary settings adequately diagnosed and treated sleep problems in this population. As a result, articles like this review by Manni and colleagues are important for disseminating the collected wisdom on managing sleep disorders in this patient group.

The authors review the polysomnographic findings that have been reported in PD and discuss how sleep disorders appear to be directly related to the pathophysiology of this condition. They provide evidence showing that this disorder often affects a number of key brainstem and hypothalamic areas that are related to sleep. Notably, the authors hypothesize that the hallucinations that often occur in PD patients may be a manifestation of pathology affecting such sleep systems.

From a clinical point of view, the authors stress the need for clinicians to be aware of the types of sleep disorders experienced in this population. Insomnia is the most common sleep complaint in PD patients, reported by approximately 30% of patients, and daytime sleepiness, nightmares, and vivid dreams are also common. In addition, the authors

estimate that 25–30% of PD patients have rapid eye movement behavior disorder (RBD). Of particular note, they indicate that RBD may herald the onset of PD and predate diagnosis by several years. Also of clinical importance, the authors highlight that sleep problems may frequently be caused by comorbid conditions, such as major depression, and the medications taken by PD patients. At low dosages, agents that increase dopamine activity, mainstays in the management of this condition, facilitate sleep; however, in higher dosages they appear to inhibit sleep. The drugs can also improve sleep through having a therapeutic effect on motor system-related sleep problems such as restless legs syndrome and periodic limb movements in sleep. Finally, the authors stress the need for evaluating sleep in PD patients and suggest the use of scales and questionnaires such as the PD Sleep Scale. They further advocate implementing combined pharmacological and behavioral therapies in those found to have sleep disorders and considering lowering dopaminergic medications if these are believed to be adversely affecting sleep.

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Sleep disorders in women: clinical evidence and treatment strategies

Soares CN, Murray BJ.
Psychiatr Clin North Am 2006;**29**:1095–113.

Insomnia occurs more frequently in women than in men, and its prevalence increases with age. This article describes changes in insomnia and other sleep disturbances associated with the menstrual cycle, pregnancy, and menopause. The authors identify potential causal mechanisms of insomnia in women, and describe diagnostic guidelines and treatment strategies.

Insomnia is more common in women than in men. In women, age-related increases in insomnia may occur due to physiological and psychosocial changes accompanying transitions in a woman's reproductive capacity. Mixed findings have been reported concerning changes in sleep across the menstrual cycle, with some evidence for insomnia and hypersomnia in the premenstrual phase. The effects of sex hormones on the suprachiasmatic nucleus also have been suggested to affect sleep.

Evidence is cited for substantial sleep disturbances during pregnancy with an increase in the prevalence of sleep-disordered breathing (SDB) and restless legs syndrome (RLS) during the third trimester. Sleep complaints can persist *post partum* due to childcare pressures, hormonal, and mood changes.

The authors report that insomnia during the menopause may be exacerbated by hot flashes; however, the efficacy of hormone therapy (HT) for insomnia during menopause is unclear. Menopausal decreases in progesterone can cause SDB, which often goes unrecognized in this patient group.

Soares and Murray suggest that diagnosis of sleep disturbances in women requires:

- A thorough interview with both patient and, if possible, their bed partner.
- History and physical examination, taking into account psychiatric complaints, hormonal status, and symptoms of RLS and SDB.
- Assessment of typical sleep behavior and sleep hygiene.

Sleep restriction and stimulus control are highlighted as effective behavioral therapies for insomnia. In terms of herbal supplements, black cohosh is identified as showing promise for some menopausal symptom relief, but not yet for insomnia; mixed evidence is reported for the use of valerian–hops. The authors report that HT reduces hot flashes in menopausal women, and perhaps insomnia and SDB, but is also associated with an increased risk of adverse outcomes. Antidepressants may improve sleep in peri- and postmenopausal women. No studies have examined the use of benzodiazepines for the treatment of insomnia in menopausal women; however, the authors report that the non-benzodiazepine receptor agonists zolpidem and eszopiclone have improved sleep in women at different stages of menopause.

Sleep and its disorders in older adults
Cooke JR, Ancoli-Israel S.
Psychiatr Clin North Am 2006;**29**:1077–93.

Sleep complaints are common in older adults. The present article describes age-related changes in sleep and the nature and correlates of sleep disturbance in the elderly, as well as providing treatment recommendations.

Adults experience numerous changes in sleep with increasing age. The authors report that older adults spend more time in bed but less time asleep, take longer to fall asleep, wake up earlier, and have more fragmented sleep than younger individuals. Time spent in the earlier sleep stages increases with age, while time spent in rapid eye movement sleep decreases. In spite of these changes, the need for sleep does not decrease with age.

The authors explain that insomnia (difficulty initiating or maintaining sleep) is the most common sleep complaint among older adults, affects women more frequently than men, and is frequently comorbid with medical problems (e.g. chronic pain, heart disease, pulmonary disease, arthritis, diabetes, nocturia), psychiatric disorders (e.g. depression, anxiety), and acute stressors. Many medications (e.g. β-blockers, corticosteroids, diuretics, bronchodilators) can also cause or exacerbate insomnia.

Cooke and Ancoli-Israel recommend behavioral interventions such as improving sleep hygiene, stimulus control, sleep restriction, and cognitive-behavioral therapy for the treatment of insomnia in this population. They report that short-acting non-benzodiazepines (e.g. eszopicline, zaleplon, and zolpidem), and the melatonin agonist ramelteon, have also proved efficacious for the treatment of insomnia in this cohort, while that the 2005 National Institutes of Health Conference on Insomnia found that there was no consistent evidence supporting safe or effective use of sedative–hypnotics, antipsychotics, antidepressants, anticonvulsants, or anti-histamines for the treatment of insomnia in older adults.

The authors note that circadian rhythm disorders (CRDs), such as advanced sleep phase (early evening sleepiness and early morning awakening) are common in older adults, and result from changes in the suprachiasmatic nucleus (SCN; a neural clock in the anterior hypothalamus) as well as decreased exposure to bright light, by which the SCN is "set". Treatment for CRDs involves exposure to bright light (sun or lightbox) at specific times of day; melatonin can also be effective. In addition, as many as 81% of older adults are reported to suffer from sleep-disordered breathing, which is associated with snoring, insomnia, daytime dysfunction (including cognitive impairment), and cardiovascular disease. Continuous positive airway pressure is the most common therapy for this condition, but tolerance to this treatment is poor.

Sleep-related problems among children and adolescents with anxiety disorders
Alfano CA, Ginsburg GS, Kingery JN.
J Am Acad Child Adolesc Psychiatry 2007;**46**:224–32.

The frequency of various sleep-related problems (SRPs) and their relationship with age, gender, and aspects of anxiety disorders, including anxiety severity and impaired daytime functioning, was examined in this investigation. The impact of pharmacological treatment in reducing SRPs in children and adolescents was also analyzed.

A multitude of research in adults has shown relationships between psychiatric disorders and sleep disturbance, with anxiety disorders exhibiting a pronounced relationship. These relationships have also been demonstrated in the pediatric population. Understanding the early mechanisms of psychological disorders and the impact they have on sleep may aid in uncovering the complex interactions of these disorders with the sleep system.

A double-blind, placebo-controlled, clinical trial of fluvoxamine was performed in a group of 128 children, aged 6–17 years, who met criteria for either generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and/or social anxiety disorder (SOC). Data were collected using several psychological assessment scales rating anxiety, behavior, functional impairment (both inside and outside of the home), and sleep-related problems (SRPs). These data were analyzed using both parent and clinician assessment.

SRPs included refusal/reluctance to sleep alone or to sleep away from home, insomnia, nightmares, being overtired, sleeping less or more than others, and talking or walking during sleep. Children were scored as having between zero and eight SRPs.

Since many children in this study had been diagnosed with more than one anxiety disorder, the results were divided into six groups of children with or without GAD, SAD, and SOC. The overall results showed that 88% of the sample reported at least one SRP and 55% reported ≥3. Children with GAD and SAD (98% and 97%, respectively), had at least one SRP and were more likely to experience insomnia than children without these disorders. Out of the children with SOC, 90% had at least one SRP; however, overall, these children had fewer SRPs and were less likely to exhibit refusal/reluctance to sleep away from the home or alone. SRPs significantly correlated with impairment measures. Furthermore, the authors found that fluvoxamine significantly reduced SRPs (insomnia, and reluctance/refusal to sleep alone) after 8 weeks of treatment.

Sleep disturbance is frequently experienced by adults and children during the course of many psychological disorders, and research has shown that the treatment of insomnia will often improve some symptoms of certain psychological disorders, such as depression. Recent studies have also revealed that the treatment of insomnia aids the improvement of anxiety disorders in an adult population. It is therefore important in a clinical setting to treat not only the psychological disorder, but also the sleep disturbance.

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Characterizing sleep in children with autism spectrum disorders: a multidimensional approach

Malow BA, Marzec ML, McGrew SG et al.
Sleep 2006;**29**:1563–71.

The study authors' examined the relationship between parental reports and objective measures of sleep and daytime behavior, including autism symptomatology, in children with autism spectrum disorders.

Autism spectrum disorder (ASD) is estimated to affect 3.4 of every 1000 children aged 3–10 years, and 40–80% of parents of children with ASD report that their child experiences some type of sleep problem.

A total of 31 children, aged 4–10 years, without a history of medication use or epileptic seizures, and in the absence of mental retardation, were enrolled in this study. Each child with ASD was classified as either a poor (n=11) or good sleeper (n=10). Ten children, also aged 4–10 years, made up the control group of typically developing children. This group was comprised of good sleepers in order to determine the role of ASD in behavioral and sleep measures, independent of being good or bad sleepers. Parents were asked to rate sleep habits and complete the Child Behavior Checklist. A clinical evaluation of sleep history was performed and the Autism Diagnostic Observation Schedule (ADOS) was used to validate the ASD diagnosis. Sleep diaries were also recorded prior to two nights of polysomnography (PSG) in the laboratory.

Children with ASD and reported poor sleep had significantly longer sleep latency and lower sleep efficiency than the other groups on night 1 in the sleep laboratory. Rapid eye movement (REM) sleep was decreased and stage 3–4 sleep increased compared with the other groups. However, night 2 did not reveal any significant differences among the groups. The group of children with ASD who were poor sleepers scored highest for affective problems. Attention problems did not differ between ASD children who were good or poor sleepers. ASD children who were poor sleepers also had worse scores on reciprocal social interaction items, based on the ADOS.

Relationships between objective PSG results and parental reports of sleep in children with ASD are sparse in the literature. The current investigators examined these relationships and found that ASD children with reported poor sleep showed greater difficulty in falling asleep and staying asleep on PSG recordings. Interestingly, the findings show ASD children with good sleep to be comparable to the control group. The results of this study indicate a relationship between ASD and sleep variables, suggesting that further investigation in this area is warranted.

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INSOMNIA

Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial

Soares CN, Joffe H, Rubens R et al.
Obstet Gynecol 2006;**108**:1402–10.

Perimenopausal and early post-menopausal years have frequently been associated with an increase in insomnia; this study aimed to test the efficacy of eszopiclone in this population. Significant improvements were seen in sleep scores as well as in measurements of quality-of-life and daytime function.

This double-blind, placebo-controlled investigation enrolled 410 women who met the entry criteria of insomnia temporally associated with the menopausal transition. Daily sleep data were collected and several ratings scales, including the physician global assessment of menopause, a menopause-specific quality-of-life questionnaire, the Greene climacteric scale, the Montgomery Asberg Depression scale, and the Sheehan Disability scale, were used to assess individuals before and at the end of treatment.

Approximately 77% of the subjects were white, 15% were black, and 8% Hispanic. The study itself involved a 7-day placebo run-in, 4 weeks of treatment with eszopiclone or placebo, followed by a 7-day placebo run-out period.

The eszopiclone group showed significantly shortened sleep latency, less wake-time after sleep onset, and improved total sleep time compared with placebo (p<0.05). At week 4, significantly more eszopiclone-treated patients were without clinically significant insomnia compared with those receiving placebo (58% vs. 35%, respectively; p<0.001). Patients receiving the active drug also reported fewer awakenings due to hot flushes compared with the placebo group. The authors hypothesize that eszopiclone may decrease the awareness of nocturnal hot flushes and increase the threshold for awakenings when those flushes occur, since no significant difference was seen in the incidence of daytime hot flushes between the two groups. Patients treated with eszopiclone reported significant improvements in mood as well as on the family/home domain of the Sheehan disability scale. No significant differences were noted in the social and work/school domains of the same scale when compared with placebo. Measures on the Montgomery Asberg Depression rating scale and the Sheehan disability scales also showed significant improvements for the active drug group.

No serious adverse events were noted during the double-blind treatment period. The withdrawal rates were 5.5% and 1.4% for active drug and placebo, respectively. The only significantly more common side-effect in the eszopiclone group was an unpleasant taste. A rebound insomnia effect was not seen after treatment discontinuation.

In contrast to a recently published study on the use of zolpidem in the menopause where sleep was improved without a parallel improvement in quality-of-life scores [1], eszopiclone-treated patients were able to show improved daytime function and quality-of-life scores in addition to the improved sleep measures.

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Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004)

Morin CM, Bootzin RR, Buysse DJ et al.
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This article is presented as follow-up to a previous article from 1999, reviewing the evidence for benefits of psychological and behavioral treatments for insomnia. Thirty-seven articles were included in the analysis and, as before, non-medication therapies produced reliable benefits in primary insomnia as well as insomnia associated with other medical and psychiatric disorders.

Since 1999, when a similar review showed benefit of psychological and behavioral treatments of insomnia, a number of additional studies have been performed seeking to clarify the effect of these non-medication therapies. The task force, commissioned by the American Academy of Sleep Medicine, identified 37 studies that met the inclusion criteria and a systemic review allowed for several follow-up conclusions.

A total of 2246 patients were enrolled in these peer-reviewed studies, with a reported overall attrition rate of <10%. Women were more heavily represented and nine of the studies focused specifically on older adults. The main sleep diagnoses were primary insomnia in 28 studies, but investigations on patients with either an associated medical disorder, psychological disorder, or both, were also included. A separate group of studies looked at hypnotic-dependent insomnia. Most used a prospective daily sleep diary to document outcome but some used the Pittsburgh Sleep Quality Index or polysomnography as one of the outcome measures. A chart listing certain parameters of all the studies reviewed is included in the article.

Primary insomnia showed a general benefit from treatment with several strategies such as cognitive-behavioral therapy (CBT), relaxation training, and sleep restriction. Frequently, a combination was more effective than a single therapy alone. The efficacy of CBT was greater than medication alone, and combination of the two produced the most benefit.

Insomnia associated with other medical or psychiatric disorders also benefited from psychological/behavioral treatments, although these improvements did not necessarily improve pain ratings, depressive symptoms, or quality-of-life measures. Chronic hypnotic users were frequently able to significantly decrease their use of medication with psychological/behavioral treatments. A greater number of studies evaluating insomnia in the elderly were available than for the previous review article, and the findings were, in general, similar to those in other population groups.

Overall, there was a trend to combine several different psychological therapies for treatment, and only a few have attempted to dismantle CBT to isolate the relative efficacy of the components.

As is reiterated in the conclusion, psychological/behavioral treatments are effective options for insomnia therapy. Importantly, these benefits were often seen even with unresolved comorbidities. An apparent limitation of many of these evaluations is the lack of a pill-placebo equivalent. The authors recommend that future studies broaden the scope of outcome measures, study the cost-effectiveness of these treatments, and that more potent interventions be found to induce more permanent complete remissions.

Lack of disseminated evidence and the fact that these therapies require a greater investment of time are two big barriers to the proper implementation of these findings.

Therapeutic options for sleep-maintenance and sleep-onset insomnia

Morin AK, Jarvis CI, Lynch AM.
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This article takes a broad look at insomnia by reviewing the medical literature from 1996 to 2006, as well as obtaining recent meeting abstracts and manufacturer's information. Starting with the basics, such as the current definitions of insomnia and its societal impact as well as reviewing sleep architecture, the authors go on to describe current thinking on pharmacological and non-pharmacological treatment options.

This extensive review was performed using a MEDLINE search of both primary and review articles in addition to the authors obtaining meeting abstracts and manufacturer's information for some of the most up-to-date data. The initial definitions of insomnia are enhanced by a review of the incidence and actual associated costs. Some polls found that more than half of US adults reported at least one symptom of insomnia at least once a week, and the economic impact in terms of factors such as work absenteeism and higher healthcare costs are estimated to be greater than US$100 billion per year.

The difference between delayed-sleep onset and early morning awakening insomnia is emphasized, along with important differences in the eventual therapeutic options. This review also notes the serious fact that insomnia is frequently both underdiagnosed and inadequately treated.

Non-pharmacological treatment strategies include stimulus control, sleep restriction, paradoxical intention, cognitive therapy, and teaching patients about sleep hygiene. While these strategies are not often used as monotherapy, they are important for those in whom medications are contraindicated or where, as is frequently the case, medications are not able to adequately and/or completely solve the sleep issues of a patient.

The pharmacological review takes each medication class into separate consideration starting with the largest group; the sedative-hypnotics. A chart classifies these drugs according to parameters such as duration of action, half-life, and most appropriate insomnia indication. With the large number of choices in this class, the chart, and further details describing the pros and cons of each treatment, help simplify making real-life medication decisions for our patients.

The melatonin receptor agonist, ramelteon, is also extensively reviewed both in its pharmacology and its application. Other prescription therapeutic options are addressed, such as the frequently utilized trazodone, which lacks substantial evidence supporting its use in insomnia. The investigational agent indiplon, a sedative-hypnotic, is also described

The authors complete the assessment of medication efficacy by reviewing data on over-the-counter therapies. It is important to realize that "over-the-counter" does not necessarily mean safer, gentler, or with lesser side effects. The data on these agents are often less extensive, and caution is advised.

In its conclusion, the article emphasizes the burden of insomnia, reviews the multitude of therapeutic strategies, and stresses the importance of an appropriate assessment of the disorder in order to make a tailored therapeutic decision for the patient.

Although a very detailed and thorough review, one of the topics perhaps not emphasized enough is the important role that comorbidities play in insomnia. Not addressing

these comorbidities, such as sleep apnea, depression, and arthritic pain, may make the insomnia itself much harder, if not impossible, to treat.

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Nonpharmacologic strategies in the management of insomnia

Yang CM, Spielman AJ, Glovinsky P.

A substantial amount of literature supports the use of non-pharmacological therapies to treat insomnia. The present article provides a theoretical rationale for the use of these interventions, and describes several non-drug approaches to this common clinical problem.

Sleep is governed by a homeostatic system that maintains equitable distribution of sleep across nights; a circadian system, which maintains an approximate daily sleep–wake rhythm; and an arousal system, which increases alertness. Insomnia results from dysfunction in one or more of these systems and/or behavioral and psychological factors (e.g. stress, maladaptive cognitions concerning sleep, poor sleep hygiene).

Numerous non-pharmacological interventions for insomnia exist. Stimulus control interventions are designed to establish an association between bedtime cues (i.e. lying in bed) and sleep, rather than arousal. Patients are encouraged to leave the bed if they are not asleep after 20 min, and to spend time performing a relaxing out-of-bed activity until they become sleepy, at which point they are to return to bed for another 20 min, and so on.

Sleep restriction therapy exploits the tendency for the drive to sleep to increase with sleep deprivation, thus improving sleep consolidation and circadian rhythm. The patient's average sleep time is determined from a sleep diary, and instructions are given to spend only as much time in bed as is typically spent asleep. Daytime napping is to be avoided.

Relaxation training can reduce waking arousal, thereby improving sleep. Progressive muscle relaxation, biofeedback, guided imagery, and other arousal reduction techniques can be used. The authors highlight the importance of in-office training, and the need for patients to practice skills at home.

Cognitive-behavioral therapy can be used to correct maladaptive cognitions and sleep hygiene education should be initiated to correct practices that compromise sleep. The authors recommend chronotherapy for patients with a delayed sleep phase and resulting late bedtime. In chronotherapy, bedtime is systematically delayed (e.g. by 3 h/night), until it occurs at a desirable time. Bright light therapy is also suggested as an effective means of shifting a patient's sleep phase.

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RESTLESS LEGS SYNDROME

Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome

Kushida CA.

The underdiagnosis of restless legs syndrome (RLS) makes it difficult for this common cause of sleep disturbance to be appropriately addressed. This article reviews the accepted definitions, characteristics, and incidence of RLS, its subtypes and diagnostic strategies, as well as a differential diagnosis of the condition.

According to some surveys, restless legs syndrome (RLS) is only appropriately diagnosed 25% of the time. A wide range of misdiagnoses are frequently given and even when the correct diagnosis is made, the treatment is often not appropriate. The lack of familiarity with the entity itself, and the fact that it is often not recognized as clinically significant, are both diagnostic barriers.

Not only are the symptoms of RLS themselves distressing, but since they may also result in sleep deprivation, RLS can contribute to many other health problems. The author reviews common clinical symptoms that help diagnose RLS and distinguish it from other diagnostic entities. RLS occurs in a circadian pattern, with patients reporting an inability to remain at rest with an internal urge to move and immediate relief of that urge as long as the limb is being moved. A US National Institutes of Health diagnostic workshop revised and updated these diagnostic criteria in 2002. The differential diagnosis includes neuropathic pain, peripheral neuropathy, arthritis, nocturnal leg cramps, restless insomnia, painful legs and moving toes, vascular insufficiency, and drug-induced akathisia.

Over 50% of RLS patients have a family history of the disease. RLS incidence increases with age and is more common in women than in men. It is associated with lower income levels, smoking, diabetes mellitus, and low levels of exercise.

Early versus late-onset as well as primary and secondary RLS are discussed and the article reiterates important differences in RLS that set it apart from other disorders with which it is frequently confused. Period limb movements in

sleep (PLMS) are specifically addressed because of the frequent misdiagnoses between these conditions; as many as 85% of RLS patients actually experience PLMS, but the two entities are not necessarily linked.

The patients' history (i.e. physical symptoms and physical examination) remains the mainstay of diagnosis since laboratory tests are, in general, not useful in the diagnosis of primary RLS. Certain comorbidities, such as sleep disturbance, depression, and neuropathies are also addressed, although specific medication treatment strategies were beyond the scope of this report. As discussed by the author, clinicians can reduce the burden of this disease by familiarizing themselves with the up-to-date diagnostic strategies.

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WAKE DISORDERS

Recent advances in the treatment and management of excessive daytime sleepiness
Black J, Duntley SP, Bogan RK et al.
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This roundtable discussion examined the prevalence, impact, diagnosis, and causes of excessive daytime sleepiness, and discussed possible treatment options including improved sleep hygiene, mechanical treatments, and wake-promoting medications.

Sleepiness that interferes with an individual's ability to function is estimated to affect between 7 and 25% of the population [1,2]. Excessive daytime sleepiness (EDS) can be caused by many factors including insufficient sleep, disorders of the circadian rhythm, sleep disorders such as obstructive sleep apnea (OSA), and central nervous system-related disorders or pathology.

Poor concentration, tiredness, fatigue, lack of energy, impaired alertness, and memory disturbances are often symptoms, and can lead to a low self-esteem as well as comorbid medical and psychiatric problems and safety concerns. The consequences of EDS range from a decreased performance at school or work, interpersonal difficulties, and social stigma to decreased cognitive functioning, an increased risk of accidental injury, and poorer quality of life. Assessment of EDS is usually performed using the self-administered Epworth Sleepiness Scale questionnaire. Medical and psychiatric issues are considered and the Multiple Sleep Latency Test (MSLT) is often used to assess for intrinsic sleepiness. Treatment methods for this syndrome include improving sleep hygiene to help prevent curtailed or impaired sleep, mechanical treatments, such as continuous positive airway pressure, for those who suffer from sleep-disordered breathing, and surgery, such as uvulopalatopharyngoplasty, can also be performed to treat mild OSA and snoring, thereby improving a patients sleep.

Bright light therapy is sometimes provided for those with disorders of the circadian rhythm and is among the methods used to combat shift work sleep disorders in those with shifted circadian rhythms. Pharmacological medications can be used to enhance alertness and awakeness during the wake period and to improve sleep duration and quality when desired. Drugs including traditional stimulants, the monoamine oxidase inhibitor selegiline, modafinil, and sodium oxybate can be used, along with treatment of the underlying cause of EDS.

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Circadian control of the sleep-wake cycle
Beersma DG, Gordijn MC.
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A number of external influences affect the pattern of wakefulness and sleep indicating alternative 24-h rhythms that are not related to the circadian pacemaker. These differences can be investigated using forced-desynchrony and constant routine experiments to evaluate the attributable influence of the pacemaker. In this review article Beersma and Gordijn investigate the two current models of 24-h sleep-pattern behaviour: the two-process model and the opponent process model. (A third process accounting for "sleep intertia" has been postulated).

Briefly, the opponent process model defines the theory that the increasing need for sleep during waking is counteracted by a circadian process that increasingly stimulates wakefulness during daytime for diurnal species, and *vice versa*. The two-process model considers the alternation of wakefulness and sleep to result from the interaction of two processes: S, which represents sleep need and is affected by behavioural states, and C, which is totally controlled by the circadian pacemaker.

This review mainly focuses on the two-process model, but the limitations of both are analyzed. One such disadvantage of these models is their deterministic nature, which cannot account for short naps or night-time waking. The opponent process model provides a better explanation

for these, but neither model fully accounts for them. In addition, both models are largely theoretical with no satisfactory measurable values.

New developments in the understanding of processes S and C are identified. Physiological processes thought to require sleep – and therefore one would expect to be correlated with process S – such as immunity, and glycogen and hypocretin metabolism, show no convincing affects. However, adenosine regulation appears to be more closely related. Similarly, memory consolidation is found to profit from sleep, a process sure to be affected by findings showing increased synaptic connectivity during waking.

Increased comprehension of the circadian system has improved our knowledge of process C, although views have been changed over time. Understanding of the supra-chiasmatic nucleus (SCN) has also altered; evidence that the SCN consists of many types of pacemaker cells with their own periods indicates subgroups of periodicity within cell clusters. Such subgroups may explain behavioural characteristics and individual differences in sleep duration. Light is considered the main zeitgeber that synchronizes the master circadian oscillator and its intensity appears to be an important factor. Indeed, an interesting study on Alzheimer's patients in a retirement home saw increased daytime light intensity reducing incidents of night-time wandering and daytime napping [1]. Physiologically it would appear that this intensity is received by a third type of photoreceptor localized to the ganglion cell layer of the retina.

Thus, an interaction between processes S and C exists as a result of behavioural activity reducing light exposure – and subsequently activity in subgroups of the SCN.

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Sleepy driver near-misses may predict accident risks

The authors investigated the prevalence of near-miss sleepy driving accidents and their association with actual driving accidents through a self-report, online questionnaire. A significant association was seen between self-reported sleepy near-miss accidents and an actual accident. The authors recommend further research into this area.

A number of recent studies have focused on the relationship between drowsy-driving and the risk of accidents; however, the majority of these have excluding the near-misses had by drowsy drivers and therefore an association between these and an actual sleepy-driving accident has not previously been reported.

The authors of this study analyzed results of an internet-based survey to determine the self-reported rates of sleepy near-miss accidents, self-reported accidents, and actual sleepy accidents among subjects answering an online US Dateline NBC News quiz.

Subjects were a mean of 37.2 (SD 13) years of age, 55% were female, 87% were white, and 53% were married. During the 3 years prior to the survey, 10.6% reported 1 near-miss accident, 5.9% reported 2–3, and 1.8% reported ≥4 near-miss accidents associated with being sleepy. A total of 18.3% self-reported a sleepy near-miss accident compared with 1.3% who reported an actual sleepy accident.

An association was seen between the age of the individual and the number of sleepy accidents; for each 10 years increase in age, a reduction of 0.77 of the rate of sleepiness-related accidents for those 10 years younger was seen – the data also showed similar results for sleepy near-miss accidents. Those who were unmarried were more likely to experience an accident or near-miss accident associated with sleepiness (2.15-fold and 1.46-fold increase compared with the rate seen in those who were married, respectively).

Data from those individuals suffering from a sleep-disorder reported a significant association with actual and near-miss sleepy accidents. Narcolepsy, in particular, had a high associated odds ratios (3.99).

The authors conclude that this study confirms the findings of other investigations of an association between daytime sleepiness, sleep disorders, driving variables, and sleepy accidents, and that these data demonstrate a similar relationship with respect to sleepy near-miss accidents. An independent dose-response relationship was determined between daytime sleepiness (as measured by the Epworth Sleepiness Scale) and near-miss sleepy accidents, and between sleepy near-miss accidents and actual accidents.

The authors acknowledge a possible selection bias of the sample and the fact that the study was not performed in a population-based cohort; however, the large number of participants (>35 000) serves to strengthen the generalizability of the study. They conclude that further investigation into the relationship between sleepy near-miss accidents and actual accidents should be performed.

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Sleep Medicine 2007

Scottsdale, AZ, USA, January 18–21, 2007

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Fourteen lectures covering current concepts in sleep medicine and several workshops on polysomnography were presented by fifteen faculty members at Sleep Medicine 2007. Content areas included aspects of diagnosis, management, and consequences of obstructive sleep apnea (OSA), restless legs syndrome, narcolepsy, insomnia, circadian rhythm disorders, and pediatric sleep disorders. Special topics included bruxism, sleep in the elderly, treatment of obesity, sleep and the esophagus, sleep in women, portable monitoring for sleep disorders, medico-legal aspects of OSA, and coding and reimbursement for sleep studies and clinic. A number of highlights of the conference are detailed below.

Pharmacological treatments of insomnia

James Parish (Mayo Clinic, Scottsdale, AZ, USA) reviewed the pharmacological treatment of insomnia. A meta-analysis of benzodiazepine medications indicated that they decreased sleep latency only slightly but increased total sleep duration by approximately 1 h. However, these drugs have been associated with daytime drowsiness and dizziness – the residual sedation is related to the metabolic half-life and presence of active metabolites.

The newer non-benzodiazepine drugs such as zolpidem, zaleplon, and eszopiclone, which bind to the benzodiazepine receptor but are short-acting, are less likely to cause daytime drowsiness or respiratory depression. Ramelteon, a melatonin receptor agonist, was approved by the US Food and Drug Administration for the treatment of insomnia in 2005. It acts through the MT1 and MT2 receptors in the brain and shortens sleep onset latency and increases total sleep time [1]. Ramelteon appears to have a minimal, if any, risk for tolerance, abuse, or rebound insomnia, and does not cause respiratory depression.

All patients with chronic insomnia would benefit from instruction on good sleep hygiene and should be evaluated for underlying causes of insomnia that may need specific therapy. Although behavioral therapy is effective over the long-term and should be offered to all patients, the use of short-acting hypnotics may provide more rapid benefit.

Tolerance has not been a limiting factor in the use of the newer agents for insomnia, and no evidence of tolerance was found in a 6-month controlled trial of eszopiclone treatment followed by a 6-month period of open-label administration [2].

OSA and cardiovascular disorders

Virend Sommers (Mayo Clinic, Rochester, MN, USA) presented mechanisms by which OSA may cause cardiac and vascular dysfunction. Sympathetic nervous system activation is present even during wakefulness in individuals with OSA, and this is further enhanced by the hypoxia and hypercapnia induced by apneas. Peaks of blood pressure occur at the end of apneas and stress from blood pressure elevation may lead to cardiac and vascular damage. C-reactive protein is elevated in OSA patients, suggesting a systemic inflammatory process that could facilitate binding of activated white cells to endothelial cells, increasing permeability to low-density lipoprotein [3]. Some studies have suggested that OSA impairs nitric oxide (NO) production in the endothelium of small arterioles, resulting in impaired dilation of these resistance vessels [4]. Others suggest that release of endothelin, a potent vasoconstrictor, may also be increased in OSA [5]. Although preliminary, these data suggest mechanisms linking OSA and increased vascular resistance and blood pressure. Insulin resistance has also been associated with OSA, and weight gain is common in the year prior to diagnosis. Promotion of obesity may therefore also be a factor by which OSA increases the risk of cardiovascular disorders.

Finally, the high negative intra-thoracic pressures generated by inspiratory efforts with an occluded upper airway increase cardiac wall stress by increasing transmural pressure. This may contribute to abnormal cardiac function, including the atrial arrhythmias associated with OSA. A recent study found that sudden cardiac death occurs much more commonly during the period 12 AM–6 AM in patients with OSA than in the general population [6]. Relative risk for a sudden cardiac death during this period was 2.6 for those with an apnea/hypopnea index (AHI) of ≥40.

Obesity and OSA

Neil Freedman (Sleep and Behavior Medicine Institute, Bannockburn, IL, USA) discussed the issue of obesity. A realistic expectation of a 5–10% weight loss over the initial 3–6 months of a diet period is important in order to avoid discouragement, and although no single weight loss diet has been found that is appropriate for all patients, a reduction in calories appears to be the essential component of any successful dietary program. Exercise should be part of all weight loss programs, but must be accompanied by caloric restriction to be effective. Two drugs are currently approved for long-term use in weight reduction programs: orlistat decreases fat absorption while sibutramine, a selective serotonin reuptake inhibitor, reduces food intake. However, drug therapy alone is not effective. Dr Freedman noted that although the 2006 American Academy of Sleep Medicine Practice Parameters for Medical Therapy of OSA indicates that successful dietary weight loss may improve the AHI and may be adjunctive in treating obese patients with OSA, there are few studies addressing weight loss as primary therapy for this condition [7]. Studies with small numbers of subjects whose mean AHI score was in the severe range reported significant reductions in AHI after dietary weight losses of 8–21%, but average post-weight loss AHI values were still at least in the moderate severity range. Greater percentage weight losses associated with bariatric surgery were reported to result in greater reductions in the AHI, with some values falling into the normal or mild severity range.

OSA and gastro-esophageal reflux

Susan Harding (University of Alabama, Birmingham, AL, USA) presented on sleep and the esophagus. During sleep, salivary secretion is inhibited and the spontaneous swallowing rate is reduced; the clearance of acid that reaches the esophagus is thereby delayed. Transient relaxations of the lower esophageal sphincter do not generally occur during stable sleep but do occur during arousals, and thus may be more common in patients with OSA. Gastric emptying is also prolonged during sleep, predisposing to acid reflux. Snoring and daytime sleepiness, as well as insomnia, were found to be strong predictors of nocturnal heartburn in subjects in the SHHS (Sleep Heart Health Study) [8]. However, despite evidence that gastro-esophageal reflux (GER) frequently co-exists with OSA, the presence and/or severity of OSA has generally not been correlated with GER symptoms [9]. Thus, a causal association of OSA with GER is uncertain. Elevating the head of the bed by 6 inches or the use of a wedge can reduce esophageal acid contact time (ACT) by at least 30%. However, use of protein pump inhibitors may still be needed to control symptoms.

Esomeprazole 40 mg was found to provide better relief of nighttime GER symptoms compared with 20 mg of omeprazole or 30 mg of lansoprazole, while at the same 40 mg dose, prantoprazole was found to provide faster relief than esomeprazole and has a longer half-life. Continuous positive airway therapy (CPAP) therapy has also been found to reduce both nocturnal and daytime ACT in patients with OSA.

Medico-legal aspects of OSA

Brian Boehlecke (University of North Carolina at Chapel Hill, Chapel Hill, NC, USA) discussed the medico-legal aspects of OSA. Patients diagnosed with OSA are 2–7 times more likely than those without this condition to have a motor vehicle crash (MVC) [10]. A survey of 1000 people who had experienced a MVC ("crashers") found that only 1.3% had been diagnosed with a sleep disorder prior to the crash; however, 25% admitted to having driven while drowsy at least 10 times during the previous year [11]. An individual's perception of his/her daytime sleepiness, as reflected by answers on a standardized questionnaire such as the Epworth Sleepiness Scale, is often not consistent with objective measures of sleepiness such as the average time-to-sleep onset during multiple daytime nap periods or the ability to stay awake during these periods when asked to do so (Multiple Sleep Latency Test or the Maintenance of Wakefulness Test, respectively). A recent study showed that the severity of vigilance impairment after sleep deprivation appears to be a trait-like characteristic of individuals, in that some subjects perform poorly under lesser degrees of sleep deprivation while others perform well even with severe sleep deprivation [12]. It is therefore difficult for a physician to predict those patients with OSA who are most at risk for a MVC. In the US, requirements for reporting individuals with medical conditions that may impair driving to the approriate licensing authority vary by state, and many have no mandatory reporting unless a condition is specifically listed as reportable. However, physicians have an ethical responsibility to warn patients with OSA about the risks of drowsy driving and to strongly consider reporting commercial drivers who appear unable or unwilling to mitigate the risk by curtailing driving until effective treatment can be instituted. For patients with OSA, adherence to treatment with effective CPAP improves objective driving performance on driving simulators and in actual on-road testing conditions. Patients with OSA who are adherent to CPAP therapy have reduced rates of MVC's that are similar to individuals without OSA. A joint committee of the American College of Chest Physicians, the American College of Occupational and Environmental Medicine, and the National Sleep Foundation recently published recommendations for criteria for medical clearance of commercial drivers with OSA [13].

Conclusion

The breadth of topics presented highlights the profound effect that sleep and sleep disturbances have on many medical conditions. Documenting risk factors for sleep disorders and seeking signs and symptoms consistent with sleep disturbance are important components of the diagnostic evaluation of all patients.

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25th Annual Annenberg Conference of Sleep Disorders in Infancy and Childhood

Rancho Mirage, CA, USA, January 25–27, 2007

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The 25th Annual Conference of Sleep Disorders in Infancy and Childhood, held January 25–27, 2007 in Rancho Mirage, CA, USA, was sponsored by the Annenberg Center for Health Sciences at Eisenhower. The 2007 Program Chair, Valerie G Kirk (Alberta Children's Hospital, Calgary, AB, Canada) welcomed attendees, reminding us of the theme of this year's meeting, "Then and Now", which celebrated the progression of the Annenberg Conference from focusing almost exclusively on infant apnea and home monitoring of infants at risk for Sudden Infant Death Syndrome (SIDS) when it first began in 1982, to becoming more inclusive, presenting the latest research coupled with practical information on sleep in infants and children.

The conference was attended by 237 people, mostly physicians, but also a sizeable number of nurses, polysomnographic technologists, and respiratory therapists. Annenberg strives to be an international meeting, inviting speakers and welcoming many from the UK, Australia, Canada, and across the European Union. Over 2.5 days, lectures from 19 invited speakers covered topics ranging from cardiorespiratory development and control in infants, sleep in special pediatric populations, and evaluation of the hypersomnolent child, with interactive breakout sessions and audience participation on child-friendly polysomnography (Carol L Rosen, Case Western Reserve University, Cleveland, OH, USA), trouble-shooting in the sleep laboratory (Shelly Bohn and Leah Schmalz, Alberta Children's Hospital), effects of drugs on sleep (Rafael Pelayo, Stanford School of Medicine, Stanford, CA, USA), the role of oximetry in neonates and infants, and SIDS (both by Estelle B Gauda, Johns Hopkins University, Baltimore, MD, USA). This report details a selection of the key presentations from the conference.

Cardiorespiratory development and control in infants

Dr Gauda moderated the session on cardiorespiratory development and control in infants. The conference began with a talk by Carl Hunt (National Heart, Lung, and Blood Institute, Bethesda, MD, USA), who was part of the 1982 inaugural faculty, reflecting on the evolution of research and knowledge about SIDS and sleep. He emphasized how SIDS most likely arises from autonomic cardiorespiratory instability, triggered by a varying conjunction of environmental risk factors (such as prone sleeping, tobacco smoke exposure, thermal stress, soft bedding) interacting with genetic polymorphisms (16 polymorphisms have already been identified in victims of SIDS). Understanding how these and other not yet identified environmental and genetic risk factors interact can help detect phenotypic patterns for those at greatest risk for SIDS. He noted that while "genetics loads the gun, environment shoots the bullet" [1].

Karen Waters (University of Sydney, Westmead, NSW, Australia) then discussed her research on post-natal exposure to cigarette smoke and/or prone sleeping in piglets. These factors can induce neuropathological changes in the brainstem nuclei that regulate the normal control of breathing, especially during periods of hypoxia. Similar changes in brainstem nuclei have been seen in victims of SIDS when compared with controls. She reviewed her work using piglet models to study the effects of intermittent hypercapnic hypoxia and post-natal exposure to nicotine on brainstem N-methyl-D-aspartate (NMDA) and serotonin (5-HT) receptor expression. Her research suggested that the expression of NMDA and 5-HT receptors differs between SIDS subjects and controls, and that post-natal cigarette smoke and/or prone sleep can result in neurochemical abnormalities in brainstem nuclei that render the individual more susceptible to SIDS [2].

Maureen Lefton-Greif (Johns Hopkins University) discussed the development and dysfunction of swallowing in infants, illustrated by remarkable videos of infants aspirating. She reviewed recent research that suggests reduced laryngeal sensation may cause apnea of infancy [3], the significant relationship between reduced laryngeal sensation and dysphagia, and how treating gastroesophageal reflux disorder (GERD) in these infants can improve swallowing function [4].

The session concluded with a lecture entitled "GERD and Apnea in Neonates", given by Richard J Martin (Case Western Reserve University). He reiterated how we should "say no to GERD", particularly in preterm infants, as untreated GERD can predispose to apnea [5]. However, further research is needed to demonstrate that treating GERD reduces the number of apneas in this patient population.

Sleep in special populations

This session was moderated by Ronald E Dahl (University of Pittsburgh, Pittsburgh, PA, USA). Luci Wiggs (Oxford Brookes University, Oxford, UK) opened the session with "Behavioral Approaches to the Management of Sleep Disturbances in Children with Developmental Delay/Mental Retardation Development Disabilities". After highlighting the increased frequency of sleep disturbances in children with developmental disorders (DD), she provided a succinct review of the efficacy of behavioral therapies for treating sleep disorders in children with these conditions. She discussed the methods used by her practice to tailor behavioral interventions for sleep disorders in children with DD, and provided practical advice about treatment after failure of the first or second intervention [6].

Kyle P Johnson (Oregon Health and Science University, Portland, OR, USA) then discussed "Autistic Spectrum Disorders (ASD) and Sleep". As many as 44–83% of children with autism suffer sleep disorders, the severity of which correlates with the degree of intellectual disability. Dr Johnson reviewed recent polysomnographic studies from adults with ASD that showed significantly longer sleep latency, reduced sleep efficiency, increased wake-after-sleep onset, decreased sleep spindle density, and decreased eye movements in rapid eye movement sleep, along with studies that reported lower nocturnal melatonin secretion in this group compared with controls. Finally, he provided practical advice on treating sleep disorders in patients with ASD, summarizing the literature available for melatonin, risperidone, massage, and chronotherapy.

Dr Dahl then discussed "Sleep and Affective Disorders: Anxious, Depressed, and Bipolar Youth". He provided a conceptual framework emphasizing bidirectional relationships between sleep and affective regulation in children and adolescents. Bipolar spectrum disorders rank in the top 10 leading causes of disability worldwide; sleep difficulties in early childhood predict for the development of anxiety and depression in adolescence; and patients with persistent insomnia have a 3.5-fold increased risk for depression compared with controls. Dr Dahl highlighted how feeling unsafe in bed, easy attention to threat, and a lower activation threshold to feelings of fear can contribute to insomnia in children and adolescents. Electroencephalogram studies of sleep in children with anxiety showed increased sleep latency and nighttime cortisol release compared with control children and those with major depressive disorders. He called for further research examining the efficacy of different behavioral treatment strategies such as targeting bedtime worries, rumination, bedtime routines, and reducing competing activities [7].

Amy Wolfson (College of the Holy Cross, Worcester, MA, USA) closed the session with a well-received lecture entitled, "Educational Approaches to Management of Sleep in Adolescents' Daily Lives". She reviewed the study design of her ongoing National Institutes of Health-funded research, STEPS (Sleep Treatment & Education Program for Students) [8], examining whether a series of lectures teaching adolescents to "sleep smart" can improve their sleep quality, sleep hygiene, quality of life, academic performance, and behavior [9,10].

The hypersomnolent child

Madeleine Grigg-Damberger (University of New Mexico, Albuquerque, NM, USA) moderated this session. Emmanuel Mignot (Stanford University) presented the first lecture, "Narcolepsy – Evolution of Understanding from Bench to Bedside". He reviewed recent experimental research on the role of hypocretins in stabilizing wakefulness and arousal networks, and their regulation of food intake, energy expenditure, modulation of addiction, and decrease in sympathetic tone, noting that human narcolepsy with cataplexy is an acquired neurodegenerative disease. Dr Mignot then discussed novel future therapies for narcolepsy including H3 antagonists, modafinil analogues, intravenous immunoglobulins, and hypocretin replacements.

"Evaluating the Hypersomnolent Child" was presented by Dr Grigg-Damberger, who emphasized circadian rhythm sleep disorders and insufficient sleep as common causes of hypersomnia in children and adolescents, and discussed how salivary dim-light melatonin onset tests can be useful in confirming phase delay or phase advance. She warned that multiple sleep latency tests (MSLT) are often initially false-negative in childhood-onset narcolepsy. The clinical and diagnostic features of other symptomatic hypersomnias (Neimann-Pick type C, Prader-Willi, myotonic dystrophy, craniopharyngiomas) were also reviewed, along with the use of cerebrospinal fluid hypocretin-1 levels to confirm human narcolepsy with cataplexy in cases where psychotropics cannot be stopped, in young or neurologically compromised children who cannot perform MSLT, or in cases where treatment has failed.

Dr Pelayo closed the session with a discussion of "Treatment Strategies for the Hypersomnolent Child", including the efficacy of sodium oxybate and modafinil

in treating childhood narcolepsy, the effectiveness of continuous positive airway pressure, orthodontics, and mandibular distraction surgeries in refractory childhood obstructive sleep apnea, and the role of iron supplements, dopamine agonists, and reduction of caffeine intake in childhood restless legs syndrome.

Closing Day Award Lectures

The first award lecture was presented by Jennifer Lowden (University of Calgary), recipient of the Professor Andre Kahn Young Investigator Award, who summarized her research on "Prenatal Cigarette Smoke Exposure Attenuates Recovery from Hypoxic Challenge in Preterm Infants". She reported that infants exposed to cigarette smoke had more breathing pauses from hypoxic challenges from which they were unable to recover compared with controls. Patricia Franco (Claude Bernard University, Lyon, France) gave the 2007 Annenberg Award Lecture, "Sudden Infant Death Syndrome: From Epidemiology to Pathophysiology". She summarized 25 years of basic and clinical research that suggested in the case of a life-threatening challenge during

sleep, an infant either arouses and autoresuscitates or becomes a victim of SIDS. The day closed with succinct cutting-edge literature reviews by Drs Estelle Gauda, Ronald Dahl, and Valerie Kirk. The 26th Annenberg Conference will be held on January 17–19, 2008.

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