The Challenges of Modern Day Work Schedules: Effects on Alertness, Performance, Safety, and Health
Melissa M Mallis, Summer L Brandt, and Mark R Rosekind

Hormonal Controls of Sleep
Axel Steiger

The Interactions Between Sleep, Metabolism, and Obesity
Shahrad Taheri

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Aims and Scope

The International Journal of Sleep and Wakefulness is designed to bring a critical analysis of the world literature on sleep disorders, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of the treatment of sleep disorders across the global healthcare system by providing an active forum or the discussion of clinical and healthcare issues.

Leading Articles – These major review articles are chosen to reflect topical clinical and healthcare issues in sleep disorders. All contributions undergo a strict editorial review process.

Clinical Reviews – The most important papers from the best of the international literature on sleep disorders are systematically selected by an internationally recognized panel of experts. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.

Meeting Reports – The International Journal of Sleep and Wakefulness also provides incisive reportage from the most important international congresses.

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Dear Colleagues,

Welcome to this first issue of The International Journal of Sleep and Wakefulness.

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, and its sister publication The International Journal of Sleep and Wakefulness – Primary Care, 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.

This first issue contains three articles. 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.

In the second article, Dr Steiger provides a review of the hormonal regulation of sleep, detailing the different and distinct endocrine signals that control sleep and wake. Growth hormone and corticotropin-releasing hormone interact in a reciprocal fashion and changes in the ratio between the two are thought to contribute to the differing sleep patterns seen in depression and normal aging. Further research is needed to fully determine a possible role for endocrine targets in the treatment of sleep disorders.

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.

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

Melissa M Mallis, Summer L Brandt, and Mark R Rosekind
Alertness Solutions, Cupertino, CA, USA

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.

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

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

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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
The Challenges of Modern Day Work Schedules

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 or 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>
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<tr>
<td>• Increased risk of heart disease</td>
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<td>• Increased sick days</td>
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<td>• More likely to smoke and/or use alcohol</td>
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<td>• Disruption in family/social time</td>
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<td>• Decreased quality of life</td>
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<td>• Accuracy and speed degradation</td>
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<td>• Increased subjective fatigue ratings</td>
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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.

References

Hormonal Controls of Sleep

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Hormones participate in sleep regulation, with the neuropeptides growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) interacting in a reciprocal fashion. In men, GHRH promotes non-rapid eye movement (NREM) sleep and GH release, and inhibits the hypothalamic–pituitary–adrenocortical (HPA) hormones; CRH exerts the opposite effect. Changes in the GHRH/CRH ratio in favor of CRH appear to contribute to sleep changes during depression and normal aging. However, in women, the effects of CRH are opposite to those in men. Along with CRH, somatostatin also impairs sleep, whereas ghrelin, galanin, and neuropeptide Y promote sleep. Vasoactive intestinal polypeptide is involved in the temporal organization of human sleep, and steroids also contribute to sleep regulation, with cortisol appearing to promote REM sleep. Various neuroactive steroids and estrogens also exert specific effects on sleep. Int J Sleep and Wakefulness 2007;1(3):9–19.

Sleep is a time of distinct endocrine activity. Electroencephalogram (EEG) recordings from young human subjects show that slow-wave sleep (SWS) and growth hormone (GH) surge predominate during the first half of the night, while the major proportion of rapid eye movement (REM) sleep and cortisol secretion occur during the second half of the night [1]. A bidirectional interaction exists between sleep EEG recordings and nocturnal hormone secretion. Changes in sleep pattern, such as sleep deprivation, result in changes in endocrine secretion. Likewise, changes in endocrine activity, such as hormone administration or hormonal disorders, affect sleep EEG recordings. Similar changes in sleep endocrine activity occur during normal aging and depression, namely a decrease in SWS and GH and an increase in cortisol. These observations point to the existence of common regulators of sleep and hormone secretion. Indeed, the neuropeptides GH-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) are key factors that, along with various other peptides and steroids, participate in sleep regulation (Table 1).

Hypothalamic–pituitary–somatotropic system
GH stimulates tissue growth and protein anabolism. GHRH and ghrelin stimulate the synthesis and secretion of GH; somatostatin inhibits this effect. All components of the hypothalamic–pituitary–somatotropic (HPS) system participate in sleep regulation (Table 1). GH release over a 24-h period peaks near to sleep onset, particularly in male subjects [2]. However, in women, a pre-sleep GH surge and one or more additional GH peaks are frequently seen [3]. The GH surge is widely sleep dependent and is suppressed during sleep deprivation in healthy subjects [4]. In patients with isolated GH deficiency, SWS time is shorter than in controls [5].

Growth hormone-releasing hormone
In mice, the GHRH receptor gene is found in the region of chromosome 13 and has been linked to SW activity (SWA) [6]. In rats, which are night-active, hypothalamic GHRH mRNA peaks at the onset of the light period when sleep propensity is highest [7]. Hypothalamic GHRH levels are low in the morning, increase in the afternoon, and decrease at night [8]. Calcium levels in γ-aminobutyric acid (GABA) neurons cultured from the rat fetal hypothalamus increase after perfusion with GHRH [9], and many hypothalamic GHRH-responsive neurons appear to be GABAergic. GHRH promotes sleep in various species including humans. SWS increases after intracerebroventricular administration of GHRH in rats and rabbits [10,11], after its injection into the medial preoptic area in rats [12], and after intravenous administration to rats [13]. Similarly, repetitive hourly intravenous injections of GHRH (between 10 pm to 1 AM) increase SWS and GH levels and decrease cortisol levels in young men [14]. Mimicking the pulsatile endogenous release of the peptide appears to be important, since GHRH infusion has no effect on sleep EEG [15]. Sleep promotion in males has been reported after intravenous [15,16] and intranasal GHRH administration [17]. The influences of GHRH on sleep are affected by the time of administration, age, and sex. Repetitive intravenous GHRH administration in the early morning has not been found to
prompt any major changes on sleep EEG recordings [18], and the sleep-promoting effect of GHRH is believed to be weaker in elderly men and women [19]. A sexual dimorphism in the response to intravenous GHRH has been reported in depressed drug-free patients of both sexes over a wide age range. In men, GHRH decreases levels of adrenocorticotropic hormone (ACTH) and cortisol; however, in women, levels of these hormones increase. Similarly, non-REM (NREM) sleep increases and wakefulness decreases in men in response to GHRH, whereas sleep is impaired in women [20,21]. In rats, GHRH receptor antagonists and antibodies to GHRH decrease NREM sleep [22,23]. In giant transgenic mice, GH levels are elevated, and periods of NREM sleep and REM sleep are greater during the light period compared with normal mice [24]. In dwarf rats, levels of hypothalamic GHRH and NREM sleep are lower than in controls [25]. Similarly, in dwarf homozygous (lit/lit) mice with non-functional GHRH receptors, NREM sleep and REM sleep are diminished. The data show that an association exists between GHRH deficiency and decreases in NREM sleep [26].

Sleep deprivation is the major stimulus for sleep, and GHRH participates in mediating this effect [27]. In rats, GHRH antibodies and microinjections of a GHRH antagonist into the preoptic area inhibit sleep promotion after sleep deprivation [12,23], while in humans the NREM sleep-

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species, [population]</th>
<th>Gender</th>
<th>Administration method</th>
<th>Wakefulness</th>
<th>NREM</th>
<th>REM</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHRH</td>
<td>rat, rabbit</td>
<td>M</td>
<td>icv, iv, microinjections into p.o.</td>
<td>–</td>
<td>↑</td>
<td>–/↑</td>
<td>REM↑ via GH↑</td>
</tr>
<tr>
<td>GHRH</td>
<td>humans [normal subjects, patients with depression]</td>
<td>M</td>
<td>iv, riv</td>
<td>–/↓</td>
<td>↑</td>
<td>–/↑</td>
<td>REM↑ via GH↑</td>
</tr>
<tr>
<td>GHRH</td>
<td>humans [normal subjects, patients with depression]</td>
<td>F</td>
<td>riv</td>
<td>↑</td>
<td>↓</td>
<td>–/↓</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>rat</td>
<td>M</td>
<td>icv, intrahyp</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>mouse</td>
<td>M</td>
<td></td>
<td></td>
<td>↑</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>humans [young controls]</td>
<td>M</td>
<td>riv</td>
<td>–</td>
<td>↑</td>
<td>(↓)</td>
<td></td>
</tr>
<tr>
<td>GHRH</td>
<td>humans [sleep deprived]</td>
<td>F/M</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>rat</td>
<td>M</td>
<td></td>
<td>–</td>
<td>↓/↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>humans [normal subjects]</td>
<td>M</td>
<td></td>
<td>–</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>humans [acquired GH deficiency]</td>
<td>F/M</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>chronic administration</td>
</tr>
<tr>
<td>SRIF</td>
<td>rat</td>
<td>M</td>
<td></td>
<td>–</td>
<td>↓</td>
<td>–/↑</td>
<td></td>
</tr>
<tr>
<td>SRIF</td>
<td>humans [young controls]</td>
<td>M</td>
<td></td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>SRIF</td>
<td>humans [elderly subjects]</td>
<td>F/M</td>
<td></td>
<td>↑</td>
<td>↓</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

↑: increase; ↓: decrease; –/↑ etc: controversial reports; (↑): weak effect; F: female; GH: growth hormone; GHRH: GH-releasing hormone; icv: intracerebroventricular; intrahyp: intrahypothalamic; iv: intravenous; M: male; NREM: non-rapid eye movement sleep; p.o.: preoptic area, REM: rapid eye movement sleep; riv: repetitive iv; sc: subcutaneous; SRIF: somatostatin.
promoting effect of sleep deprivation is augmented by repetitive intravenous GHRH and CRH administration during the recovery night after sleep deprivation in patients [28]. Negative feedback inhibition of GHRH by GH in animals and in humans decreases NREM sleep [26,29]; however, sleep remained unchanged after chronic GH substitution in patients with acquired GH deficiency [30]. GHRH therefore promotes NREM sleep in various species including humans, at least in males. High levels of GHRH are associated with greater amounts of NREM sleep, whereas reduced GHRH (e.g. during aging or in experiments with GHRH antagonists or antibodies) causes a decline in SWS or NREM sleep. GHRH has also been reported to participate in sleep promotion after sleep deprivation.

**Somatostatin**

Intravenous somatostatin administration impairs sleep in the elderly [31], but has no effect in young individuals [14,32]. In rats, the somatostatin analogue octreotide decreases NREM sleep and GH levels [33], and in normal young men SWS decreases and intermittent wakefulness increases after subcutaneous octreotide administration [34]. Octreotide is long-acting and more potent than exogenous somatostatin; the same dose of somatostatin that is ineffective in young men impairs sleep in the elderly, probably owing to a decline in endogenous GHRH during aging. Somatostatin inhibits GABAergic transmission in the sensory thalamus in cats and rats, and this mechanism may contribute to the decrease of NREM sleep after somatostatin administration [35]. A reciprocal interaction of GHRH and somatostatin in sleep regulation, similar to their opposite effects on GH release, appears likely.

**Ghrelin and GH secretagogues**

As with GHRH, ghrelin increases SWS and GH levels in young men [36]. However, in contrast to the decrease in cortisol seen after GHRH administration [14], ACTH and cortisol increase after ghrelin administration in men [36]. It is possible that ghrelin acts as an interface between the hypothalamic–pituitary–adrenocortical (HPA) and the HPS systems. In mice, ghrelin enhances NREM sleep only in those with an intact GHRH receptor; in animals with non-functional GHRH receptors, sleep has been found to remain unchanged [37]. Oral administration of the synthetic GH secretagogue MK-677 for 1 week has been seen to promote sleep in young men, but to only have a weak effect in elderly subjects [38]. During the recovery night after sleep deprivation, ghrelin secretion increases earlier in normal subjects compared with the baseline night [39]. These findings suggest that ghrelin is a sleep-promoting factor; however, in rats, administration of ghrelin to various hypothalamic sites increases wakefulness and feeding [40]. In one study, ghrelin levels appeared elevated in a patient with night-eating syndrome [41], suggesting that the doses of ghrelin that enhance appetite may impair sleep.

**HPA system**

The HPA system mediates the stress reaction. The effects of HPA hormones on sleep are summarized in Table 2. CRH release from parvocellular neurons of the paraventricular nucleus of the hypothalamus results in the secretion of ACTH from the anterior pituitary gland and, finally, in the secretion of cortisol (in humans) or corticosterone (in rats) from the adrenocortex.

In humans, ACTH and cortisol levels are low during the first few hours of the night. During the early morning, several pulses of cortisol secretion occur, the first between 2 AM and 3 AM, followed by further pulses until awakening [1]. The pattern of cortisol secretion is widely dependent on circadian rhythm, and manipulation of the sleep/wake pattern prompts subtle changes in HPA secretion [1].

**Sleep in disorders with pathological changes of HPA activity**

Excessive levels of cortisol are found in Cushing’s disease, and decreased SWS, disturbances of sleep continuity, and REM sleep disinhibition have been reported in patients with this condition [42]. Similar symptoms are frequently seen in depression, where the dysregulation of the HPA system is more subtle. Characteristic sleep EEG changes in patients with depression include disturbed sleep continuity, a decrease in NREM sleep, and REM sleep disinhibition (reviewed in [43]). Most sleep endocrine studies in depressed patients report elevated cortisol and ACTH (reviewed in [44]). GH was blunted in most, but not all, studies (reviewed in [44]). An intra-individual comparison of depressed adult patients who were drug-free for ≥ 14 days before each examination showed a decrease in cortisol levels between the stages of acute depression and recovery; however, sleep EEG abnormalities and low GH levels persisted [45]. Since cortisol normalizes independently from sleep, it is unlikely that hypercortisolism in depression is secondary to shallow sleep. The metabolic disturbances during acute depression appear to result in a biological “scar”, as reflected by the persistent changes in sleep EEG and GH levels after remission.

This hypothesis is further supported by findings in patients who survived severe brain injury [46]. Several months after the event their cortisol levels did not differ from those of healthy controls, but GH levels and stage 2 sleep time were reduced. Either HPA overactivity due to stress in the intensive care situation after brain injury or, in some patients, treatment with glucocorticoids, may have contributed to the changes of...
sleep EEG and of GH levels. Some [47,48], but not all [49], studies report elevated HPA hormones in primary insomnia.

During an episode of upper airway constriction in obstructive sleep apnea (OSA) syndrome, progressive hypoxemia occurs owing to asphyxia, causing autonomic sleep EEG arousal. Buckley and Schatzberg have suggested that OSA activates the HPA system through this autonomic effect, causing awakening and arousal [50]. This HPA activation may be a risk factor in the development of metabolic syndrome in patients with untreated OSA. Furthermore, they suggest that HPA overactivity may contribute to the pathophysiology of OSA in hypertension.

**CRH**

In rats, CRH gene transcription levels increase during the dark period when the animals are active, and decrease in the morning and throughout the light period [51]. In the Lewis rat, the synthesis and release of CRH is reduced because of a hypothalamic gene defect. These rats spend less time awake and more time in SWS than those without the defect [52]. Wakefulness in rats is reduced by a CRH antisense oligodeoxynucleotide [53], and, after prolonged wakefulness, CRH levels in the striatum, limbic areas, and pituitary are increased [54]. These studies suggest a role for CRH in the maintenance of wakefulness and sleep-disturbing effects. In homozygous mice overexpressing CRH in the central nervous system, NREM sleep is reduced, and wakefulness and REM sleep are elevated compared with wild-type mice. Moreover, after forced swimming and sleep deprivation, the NREM sleep rebound is reduced, and the REM sleep rebound increases in these transgenic mice compared with controls [55], suggesting a role for CRH in promoting REM sleep.

### Table 2. Effects of hormones of the hypothalamic–pituitary–adrenocortical system on sleep.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species [population]</th>
<th>Gender</th>
<th>Administration method</th>
<th>Wakefulness</th>
<th>NREM</th>
<th>REM</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH</td>
<td>rat M, iv</td>
<td>↑↓</td>
<td>–</td>
<td>↓</td>
<td>–/↓</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CRH</td>
<td>mouse M, COEM</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CRH</td>
<td>humans M, riv</td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>REM ↓</td>
</tr>
<tr>
<td>CRH</td>
<td>humans M, iv</td>
<td>↑↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CRH</td>
<td>humans M, icv</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>rat M, intranasal</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>humans M, icv</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>humans M, iv infusion</td>
<td>–</td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ACTH (4–9)</td>
<td>humans M, riv</td>
<td>↑↓</td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>humans M, iv, r iv</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>humans M, riv</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>GR agonist*</td>
<td>humans M, iv/oral</td>
<td>–</td>
<td>↑</td>
<td>SWS shift to REM latency↑</td>
<td>–</td>
<td>10 days administration</td>
<td></td>
</tr>
</tbody>
</table>
Following administration of intracerebroventricular CRH, SWS decreases in rabbits [56] and also in rats (even after 72 h of sleep deprivation in the latter) [10]. Furthermore, sleep latency and REM sleep increase [57]. Repetitive hourly intravenous CRH administration has a similar decreasing effect on NREM sleep and SWS in young men, as the GH surge decreases and cortisol levels increase [58].

In one study, administration of two different CRH antagonists, α-helical CRH-(9–41) and astressin, given to rats before the dark period, decreased wakefulness dose-dependently [59]. In contrast to another study [60], α-helical CRH was effective only in stressed animals. REM sleep was increased in these rats and decreased to the values of the non-stressed condition after receipt of the CRH antagonists. In sleep-deprived rats, α-helical CRH diminished the REM sleep rebound during recovery sleep. Stress acting via CRH is thought to be the major factor inducing the REM sleep rebound after sleep deprivation [61]. After a 4-week trial using a CRH-1-receptor antagonist, the characteristic sleep EEG changes in a sample of depressed patients were counteracted with a decrease in the number of awakenings and the REM sleep density and an increase in SWS [62]. These results suggest that:

- CRH is involved in the pathophysiology of sleep EEG changes during depression, including REM sleep disinhibition.
- CRH-1-receptor antagonism helps to treat impaired sleep.

**Vasopressin**

Vasopressin acts as the major cofactor to CRH in activation of the stress reaction. Intracerebroventricular vasopressin has been shown to enhance wakefulness in rats [63], while long-term intranasal vasopressin improves sleep in healthy elderly subjects with increases seen in total, SWS, and REM sleep time [64]. The study authors suggest that this treatment may compensate for an age-related decrease in vasopressin content in the suprachiasmatic nucleus, or that vasopressin could act by stimulating the expression of central corticosteroid receptors.

**ACTH**

Infusions of ACTH suppress REM sleep in healthy subjects [65–67], whereas levels of cortisol increase [67]. The ACTH (4–9) analogue ebiratide shares several behavioral effects of ACTH, but does not affect peripheral hormone secretion. Accordingly, one study found that after repetitive administration of intravenous ebiratide, GH and cortisol levels remained unchanged in young male controls, sleep onset increased, wake time was elevated, and SWS decreased during the first third of the night [68]. This observation corroborates the view that the blood–brain barrier does not exclude intravenously administered neuropeptides, since ebiratide induced sleep EEG changes in the absence of effects on peripheral hormone secretion.

**Cortisol, synthetic glucocorticoid, and mineralocorticoid receptor ligands**

Nocturnal infusion and pulsatile intravenous administration of cortisol increase SWS, SWA, and GH levels, and decrease REM sleep in healthy young human controls [69–71]. Similarly, SWS, SWA, and GH levels increase, and REM sleep decreases, in analogue protocols with intravenous cortisol in elderly men [72], and also in patients with depression [73]. Since CRH and cortisol exert opposite effects on SWS [58,69,70] and GH [70,72], it appears unlikely that these effects are mediated by increased cortisol. In contrast, these changes may be due to negative feedback inhibition of endogenous CRH. Because, in contrast to ebiratide, CRH [58], ACTH [67], and cortisol [69,70,74] diminish REM sleep, REM sleep suppression may be mediated by cortisol after administration of each of these hormones. Similarly, the inhibition of cortisol synthesis by metyrapone reduces SWS and cortisol in controls, whereas REM sleep is not affected [75]. It is thought that in this type of experiment endogenous CRH is enhanced, since ACTH is distinctly elevated.

In contrast to the effects of acute cortisol administration, subchronic treatment of female multiple sclerosis patients with the glucocorticoid receptor (GR) agonist methylprednisolone resulted in reduced REM sleep latency, increased REM sleep density, and a shift of the major portion of SWS from the first to the second NREM sleep period [76]. These changes resembled sleep EEG disturbances in depression. In a single case study of a young male subject after oral administration of the mixed glucocorticoid and progesterone receptor antagonist mifepristone, ACTH and cortisol levels increased and sleep was distinctly disrupted [77]. The effects of other peptides on sleep are shown in Table 3.

**Thyreotropin-releasing hormone**

Pulsatile intravenous thyreotropin-releasing hormone (TRH) decreases sleep efficiency in young male controls [78].

**Vasoactive intestinal polypeptide**

Vasoactive intestinal polypeptide (VIP) enhances REM sleep in laboratory animals [79]. When VIP is given to rats during the dark period, NREM sleep and REM sleep increase [80,81]. VIP microinjections into the pontine reticular tegmentum and the oral pontine tegmentum also enhance REM sleep in these animals [82]. Moreover, this REM sleep-promoting effect of systemic VIP is inhibited by immunoneutralization.
of circulating prolactin, and it therefore appears likely that 
stimulation of prolactin is involved in the promotion of 
REM sleep after VIP injection [83]. Systemic and intra-
hypothalamic prolactin increases REM sleep in cats, rabbits, 
and rats [84,85].

In a study performed in young men, two doses of VIP were 
seen to exert different effects [86]. After pulsatile intravenous 
administration of 4 x 10 µg VIP, prolactin decreased but sleep 
EEG remained unchanged. After 4 x 50 µg VIP, prolactin 
increased and the NREM sleep–REM sleep cycles decelerated. 
Each of the NREM sleep and REM sleep periods was 
prolonged, the cortisol nadir appeared advanced, and the GH 
surge was blunted [86]. VIP therefore appears to act on the 
circadian clock, resulting in prolonged sleep cycles and 
advanced occurrence of the cortisol nadir. The blunted GH 
surge may be related to an advanced increase of HPA activity.

**Pituitary adenylate cyclase-activating polypeptide**

After local administration of pituitary adenylate cyclase-
activating polypeptide (PACAP) into the pontine reticular 
formation of rats, REM sleep increased [87]; pulsatile 
intravenous PACAP caused the time constant of the 
physiological SWA decline to increase compared with 
controls. It has therefore been hypothesized that PACAP 
might be involved in homeostatic sleep regulation [88].

**Galanin**

Galanin is widely located in the mammalian brain. A cluster 
of GABAergic and galaninergic neurons identified in the 
ventrolateral preoptic area are thought to stimulate NREM 
sleep [89]. In the rat, sleep remains unchanged after 
intracerebroventricular galanin, but REM sleep deprivation 
stimulates galanin gene expression [90]. Repetitive

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**Table 3. Effects of other peptides on sleep.**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species [population]</th>
<th>Gender</th>
<th>Administration method</th>
<th>Wakefulness</th>
<th>NREM</th>
<th>REM</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH</td>
<td>humans [young controls]</td>
<td>M</td>
<td>riv</td>
<td>–</td>
<td>–/↑</td>
<td>–</td>
<td>SEI ↓</td>
</tr>
<tr>
<td>Prolactin</td>
<td>cats, rats, rabbits</td>
<td>M</td>
<td>icv, systemic</td>
<td>–</td>
<td>–/↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>VIP</td>
<td>rat</td>
<td>M</td>
<td>icv</td>
<td>–</td>
<td>–/↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>VIP</td>
<td>humans [normal controls]</td>
<td>M</td>
<td>riv</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>deceleration of NREM/REM cycles</td>
</tr>
<tr>
<td>Galanin</td>
<td>rat</td>
<td>M</td>
<td>icv</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Galanin</td>
<td>humans [normal controls]</td>
<td>M</td>
<td>riv</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>deceleration of REM periods ↑</td>
</tr>
<tr>
<td>Galanin</td>
<td>humans [patients with depression]</td>
<td>F/M</td>
<td>iv</td>
<td>–</td>
<td>–</td>
<td>REM latency ↓</td>
<td></td>
</tr>
<tr>
<td>NPY</td>
<td>rat</td>
<td>M</td>
<td>icv</td>
<td>–/↑</td>
<td>–</td>
<td>–</td>
<td>benzodiazepine-like changes of sleep EEG</td>
</tr>
<tr>
<td>NPY</td>
<td>humans [young controls]</td>
<td>M</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>sleep latency ↓ 1st REM period ↓ SPT ↑</td>
</tr>
<tr>
<td>NPY</td>
<td>humans [middle-aged controls and patients with depression]</td>
<td>F/M</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>sleep latency ↓</td>
</tr>
</tbody>
</table>

↑: increase; ↓: decrease; –/↑ etc.: controversial reports; EEG: electroencephalogram; F: female; icv: intracerebroventricular; iv: intravenous; M: male; NPY: neuropeptide Y; NREMS: non-rapid eye movement sleep; REMS: rapid eye movement sleep; riv: repetitive iv; SEI: sleep efficiency index; SPT: sleep period time; TRH: thyreotropin-releasing hormone; VIP: vasoactive intestinal polypeptide.
intravenous galanin increases SWS and the duration of REM sleep periods in young men, although GH and cortisol levels remain unchanged [91]. In a study where galanin or placebo was given intravenously to patients with depression during therapy with the tricyclic antidepressant trimipramine, REM sleep latency increased and the severity of depression, as measured by the Hamilton Depression Scale, decreased in those receiving the active drug [92]. These observations suggest an acute antidepressive effect of galanin.

**Neuropeptide Y**

Opposing effects of CRH and neuropeptide Y (NPY) have been described in animal models of anxiety [93]. Intracerebroventricular NPY influenced EEG spectral activity in rats in a similar way to that of benzodiazepines [94], while prolongation of sleep latency after CRH administration was antagonized dose-dependently by NPY [95]. In contrast, wakefulness increased after intracerebroventricular and lateral hypothalamic administration of NPY to rats [96]. In young males, repetitive intravenous NPY decreased sleep latency, the length of the first REM sleep period, and cortisol and ACTH levels, and increased overall sleep period time and stage 2 sleep [97]. In depressed patients of both sexes within a wide age range, and in matched controls, sleep latency was reduced and prolactin levels increased after NPY administration, whereas cortisol, ACTH, and other sleep EEG variables remain unchanged [98]. It is thought that NPY participates in sleep regulation, in particular as a signal for sleep onset, as an antagonist of CRH acting via the GABA<sub>A</sub> receptor.

**Gonadal hormones**

In healthy women, the percentage of REM sleep tends to be higher in the early follicular than in the late luteal phase, and the percentage of NREM sleep is higher in the luteal compared with the follicular phase. In NREM sleep, EEG power density in the upper frequency range of the sleep spindles exhibits a large variety across the menstrual cycle, reaching a maximum during the luteal phase [99]. In menopausal women, EEG activity in the sigma frequency range shows a distinct decline, whereas in men these changes occur more gradually [100]. After the menopause, sleep endocrine changes associated with depression are accentuated [101].

In a study of post-menopausal women, estrogen replacement therapy by skin patch enhanced REM sleep and reduced intermittent wakefulness during the first two sleep cycles. The normal decrease in SWS and SWA from the first to the second cycle was also restored [102]. These effects and those of progesterone replacement are shown in Table 4.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species [population]</th>
<th>Gender</th>
<th>Administration method</th>
<th>Wakefulness</th>
<th>NREM</th>
<th>REM</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>humans [postmenopausal]</td>
<td>F</td>
<td>patch</td>
<td>(↑)</td>
<td>–</td>
<td>(↑)</td>
<td></td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>rat</td>
<td>M</td>
<td>sc</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>humans [young controls]</td>
<td>M</td>
<td>oral</td>
<td>–</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>rat</td>
<td>M</td>
<td>ip</td>
<td>↓</td>
<td>–</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>humans [young controls]</td>
<td>M</td>
<td>oral</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>humans [postmenopausal]</td>
<td>F</td>
<td>oral</td>
<td>↓</td>
<td>–</td>
<td>↑</td>
<td>subchronic administration</td>
</tr>
<tr>
<td>DHEA</td>
<td>humans [young controls]</td>
<td>M</td>
<td>oral</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

↑: increase; ↓: decrease; (↑): weak effect; DHEA: dehydroepiandrosterone; F: female; ip: intraperitoneal; M: male; NREM: non-rapid eye movement sleep; REM: rapid eye movement sleep; sc: subcutaneous.
Figure 1. A model of peptidergic sleep regulation.

CRH: corticotropin-releasing hormone; GH: growth hormone; GHRH: GH-releasing hormone; NPY: neuropeptide Y; REM: rapid eye movement sleep; SRIF: somatostatin.

Reproduced from [114].

CRH: corticotropin-releasing hormone; GH: growth hormone; GHRH: GH-releasing hormone; NPY: neuropeptide Y; REM: rapid eye movement sleep; SRIF: somatostatin. Reproduced from [114].
Neuroactive steroids

Certain steroids, so-called neuroactive steroids, exert direct effects on neuronal membranes and thereby rapidly affect CNS excitability [103]. Their effect on neuronal excitability is mediated by the GABA receptors. Neuroactive steroids are involved in the regulation of anxiety, memory, and sleep, and glial cells are capable of synthesizing certain neuroactive steroids independently of peripheral steroid sources [104]. Various neuroactive steroids exert specific effects on sleep EEG in humans and rats (Table 4).

SWS increases and EEG power in the spindle frequency range decreases in healthy controls after receiving oral pregnenolone [105]. These changes resemble the effects of a partial inverse agonist at the GABA receptor. Similarly, in rats, subcutaneous pregnenolone at the beginning of the light period increases SWA [106].

A dose-dependent hypnotic effect of intravenous progesterone was reported as early as 1954 [107]. In healthy young men given oral progesterone, NREM sleep, particularly stage 2, increases, and SWA decreases [108]. Furthermore, EEG power in the higher frequency range (>15 Hz) tends to be elevated. In women, progesterone levels decline after the menopause. Subchronic oral progesterone replacement increases REM sleep and decreases intermittent wakefulness in post-menopausal women [109].

Intraperitoneal administration of three doses of progesterone at the onset of the dark period in rats prompts a dose–dependent decrease of NREM sleep latency, wakefulness, and REM sleep, and increases REM sleep latency. EEG activity decreases in the lower frequency range and increases in the higher range [110]. Intraperitoneal allopregnanolone reduced NREM sleep latency and increased pre-REM sleep in rats; in NREM sleep, EEG activity decreases in the lower frequency range and increases in the higher range [111]. These data confirm benzodiazepine-like effects of allopregnanolone on sleep.

Oral dehydroepiandrosterone (DHEA) selectively has been shown to increase REM sleep in young normal men [112]. This finding is compatible with a mixed GABA agonistic/antagonistic effect. After intraperitoneal DHEA sulfate (DHEAS) in another study, a dose–dependent effect on EEG power occurred in rats: 50 mg/kg DHEAS augmented EEG power in the spindle frequency range, whereas 100 mg/kg DHEAS exerted opposite effects [113].

Conclusion

Various hormones (particularly neuropeptides and steroids) exert specific effects on sleep EEG. A model of peptidergic sleep regulation is proposed in Figure 1. The peptides GHRH, ghrelin, galanin, and NPY promote sleep, at least in males, whereas CRH and somatostatin impair NREM sleep.

The reciprocal interaction of GHRH and CRH plays a key role in sleep regulation: GHRH promotes NREM sleep, at least in males, and stimulates GH, whereas CRH maintains wakefulness and enhances the HPA hormones. Furthermore, CRH appears to promote REM sleep. Changes in the CRH/GHRH ratio in favor of CRH contribute to the sleep endocrine changes seen during depression and aging. GHRH participates in sleep promotion after sleep deprivation; however, in women, GHRH impairs sleep. Similar to their reciprocal role in GH regulation, GHRH and somatostatin exert opposite effects on sleep in males. Along with GHRH, galanin and ghrelin promote NREM sleep, but in contrast to GHRH, ghrelin stimulates HPA activity in males. It is therefore possible that ghrelin may act as an interface between the HPA and HPS systems. Galanin, ghrelin, and GHRH may either act in a synergistic fashion or be part of a cascade resulting in the promotion of NREM sleep. It is likely that GABAergic neurons mediate their effects.

The effects of NPY, a major signal for sleep onset, also appear to be mediated via the GABAA receptor. VIP seems to participate in the temporal organization of sleep and, after VIP administration in young men, the NREM sleep–REM sleep cycle is decelerated, possibly through action at the suprachiasmatic nucleus. PACAP appears to also be involved in homeostatic sleep regulation.

It is thought that short-term administration of cortisol promotes SWS through feedback inhibition of CRH. Furthermore, short-term cortisol suppresses REM sleep in humans, whereas subchronic administration of a glucocorticoid agonist in patients with multiple sclerosis prompts sleep EEG changes similar to those in patients with depression, including REM sleep disinhibition. A synergy between elevated CRH activity and enhanced glucocorticoid levels might contribute to the sleep EEG changes in depression. GABAA receptors are also targets of various neuroactive steroids that exert specific effects on sleep. The changes in sleep EEG after the menopause and the beneficial effect of estrogen replacement therapy also suggest a role for estrogen in sleep regulation.

The effects of CRH-1-receptor antagonism in depression, of arginine vasopressin in the elderly, and of estrogen and progesterone replacement therapy in menopausal women are promising signs for the clinical application of sleep endocrine research.

Acknowledgment

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Disclosures

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References

48. Alex Steiger

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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.

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

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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,
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Design</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vioque et al., 2000 [22]</td>
<td>Spain</td>
<td>1772</td>
<td>Cross-sectional</td>
<td>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.</td>
</tr>
<tr>
<td>Shigeta et al., 2001 [18]</td>
<td>Japan</td>
<td>437</td>
<td>Cross-sectional</td>
<td>Sleeping ≤6 h was associated with BMI ≥25 kg/m² (OR 1.98, 95% CI 1.03–3.82) vs. &gt;6 h sleep.</td>
</tr>
<tr>
<td>Kripke et al., 2002 [12]</td>
<td>USA</td>
<td>1.1 million</td>
<td>Epidemiological survey; Cancer Prevention Study II</td>
<td>U-shaped relationship between sleep duration and obesity in women, but linear relationship for men from baseline sleep duration of 7 h.</td>
</tr>
<tr>
<td>Heslop et al., 2002 [10]</td>
<td>UK</td>
<td>6797 (baseline)</td>
<td>Cross-sectional analysis from cohort study</td>
<td>Short sleep duration associated with obesity at baseline and at second screening.</td>
</tr>
<tr>
<td>Taheri et al., 2004 [20]</td>
<td>USA</td>
<td>721</td>
<td>Cross-sectional; Wisconsin Sleep Cohort Study</td>
<td>U-shaped relationship between sleep duration and obesity; short sleep duration was associated with higher ghrelin and lower leptin levels.</td>
</tr>
<tr>
<td>Cournot et al., 2004 [7]</td>
<td>France</td>
<td>3127</td>
<td>Cross-sectional; Vieillissement et Santé au Travail study</td>
<td>Mean BMI was higher in women reporting sleep duration &lt;6 h vs. ≥6 h (24.4 kg/m² vs. 23.4 kg/m²); no association in men.</td>
</tr>
<tr>
<td>Patel et al., 2004 [14]</td>
<td>USA</td>
<td>82 969 (women)</td>
<td>Prospective; Nurses Health Study</td>
<td>U-shaped relationship between sleep duration and BMI in women</td>
</tr>
<tr>
<td>Hasler et al., 2004 [9]</td>
<td>Switzerland</td>
<td>496</td>
<td>Prospective; Zurich Cohort Study</td>
<td>Trend for negative association between average change in weight gain and average change rate in sleep duration.</td>
</tr>
<tr>
<td>Vorona et al., 2005 [24]</td>
<td>USA</td>
<td>924</td>
<td>Cross-sectional; primary care center-based</td>
<td>Overweight and obese patients slept less than those of normal weight.</td>
</tr>
<tr>
<td>Gangwisch et al., 2005 [8]</td>
<td>USA</td>
<td>9588</td>
<td>Cross-sectional; National Health and Nutrition Examination Survey</td>
<td>Those aged 32–49 years who slept &lt;7 h had a higher BMI vs. those who slept ≥7 h.</td>
</tr>
<tr>
<td>Singh et al., 2005 [19]</td>
<td>USA</td>
<td>3158</td>
<td>Cross-sectional, telephone interview</td>
<td>U-shaped relationship between sleep duration and obesity, but only significant for shorter sleep hours.</td>
</tr>
<tr>
<td>Patel et al., 2006 [16]</td>
<td>USA</td>
<td>68 183 (women)</td>
<td>Prospective; Nurses Health Study</td>
<td>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.</td>
</tr>
<tr>
<td>Kohatsu et al., 2006 [11]</td>
<td>USA</td>
<td>990</td>
<td>Cross-sectional survey, rural population</td>
<td>Weeknight self-reported sleep duration negatively correlated with BMI (beta=-0.42; 95% CI -0.77 to -0.07).</td>
</tr>
</tbody>
</table>

BMI: body mass index; CI: confidence interval; OR: odds ratio.
true biology signal compared to high leptin is a stronger signal for 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.

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.

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.

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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/m²; 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
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.

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

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).

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...
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...
The interactions between sleep, metabolism, and obesity 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 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.

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 not be lost.

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Disclosures

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Obesity, and not obstructive sleep apnea, is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing
Sharma SK, Kumpawat S, Goel A et al. 

Recognizing the growing issue of obesity on the Indian subcontinent, the authors of this study analyzed the metabolic profiles of obese subjects with and without obstructive sleep apnea, and of control subjects of a healthy weight.

Due to the high prevalence of obstructive sleep apnea (OSA), and the severe comorbidities with which it has been linked there is an urgent need for research into this disorder. This study adds to the literature, providing an in-depth investigation into the complex relationships between metabolic abnormalities and obesity in individuals with and without OSA.

A total of 120 subjects participated in the study; 40 obese subjects with OSA, 40 obese subjects without OSA, and 40 subjects of a healthy weight. Subjects were matched for age and sex, and the metabolic profiles of each patient were recorded, including levels of fasting blood sugar, insulin resistance, leptin, and adiponectin.

As has been reported by previous studies, there were no significant differences between OSA patients and obese controls in the various metabolic parameters analyzed. Further analysis showed no significant difference between groups in fasting blood sugar, serum insulin, leptin, or adiponectin; however, many of these parameters were worse in OSA patients compared with non-obese controls. Obesity, waist circumference, and waist–hip ratio were found to be independently associated with OSA, and obesity was also shown to be a major factor in the metabolic abnormalities evaluated on multivariate analysis.

The results indicate that there are no independent links between the specific metabolic abnormalities analyzed in this study and OSA. Unsurprisingly, obesity was found to be the major determinate of various metabolic abnormalities. Contrary to the current study, previous studies have suggested links between serum leptin levels and insulin resistance and OSA, which should be strongly considered when reviewing the data. To further confirm the current findings, the presence of morbidities such as impaired insulin regulation and higher serum leptin levels should be studied in non-obese subjects with OSA.

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Does obstructive sleep apnea affect aerobic fitness?
Guillermo LQ, Gal TJ, Mair EA. 

The principal aim of this study was to determine whether patients with obstructive sleep apnea (OSA) had objective changes in aerobic fitness, as measured by maximum oxygen consumption (VO2 max) with cycle ergometry. Data from 247 participants from the US Air Force revealed that, in general, aerobic fitness was not affected by OSA, unless the apnea–hypopnea index was >20. Furthermore, VO2 max was unaffected by either medical or surgical treatments.

Although hypersonolence is, in the majority of patients, a key symptom of obstructive sleep apnea (OSA), its residual effects on exercise tolerance have received limited attention. The authors of the present study aimed to delineate this relationship and ascertain whether medical or surgical treatment for OSA could potentially ameliorate these effects, if in fact they do exist.

Aerobic fitness, as measured using maximum oxygen consumption (VO2 max) with cycle ergometry, was recorded in a retrospective cohort of a US Air Force population comprised of 247 (88.3% male) patients with documented OSA. The data from this cohort were then compared with a large control group in a tertiary care setting. Ergometry data
from the OSA patients were also compared preceding the initial diagnostic polysomnogram (PSG) and post-treatment, after medical or surgical interventions for the OSA.

Interestingly, and unexpectedly, the majority of the patients with OSA had an increased VO$_2$ max compared with the control group. However, when the data were stratified by age, male patients with OSA demonstrated significantly lower mean ergometry values, with the exception of the groups aged 25–29 years and 45–49 years. As expected, those male patients with moderate-to-severe OSA (apnea–hypopnea indices 20–40) also demonstrated significantly lower mean ergometry values compared with the control group (p=0.0001). Surprisingly, no significant change in these values occurred when patients with OSA were treated with either medical or surgical interventions.

Although there is evidence suggesting that sleep deprivation can decrease exercise performance, this study did not show a significant association between the two, except in those patients with moderate-to-severe OSA. However, the methodology of this study is questionable since, as the authors themselves suggest, the US Air Force is not a representative cohort of patients with OSA because individuals are physically fit and may not have the classical features of a typical sleep apneic patient. The relatively young age of the patient population in this study (aged 17–54 years), also precludes generalization of these results, as does the small sample size.

Unfortunately, a sufficient or comprehensive investigation into the effects of either the medical or surgical treatments of OSA was not performed. The limited data suggest only that no differences were noted in exercise tolerance after the two types of interventions, without noting the severity of the OSA being treated or measuring continuous positive airway pressure compliance in those treated with this modality. A number of shortcomings in this study need to be broached before a consensus regarding the relationship between OSA and exercise tolerance can be reached.

The authors of the current study examined individuals with and without obstructive sleep apnea to investigate their familial risks for coronary artery disease (CAD) through analysis of various risk factors and premature CAD mortality in this group.

Within the last decade, genetic research has helped us to make vast strides in our understanding of a multitude of diseases. Identifying familial links in diseases is often the first step in determining whether genetic links indeed exist.

A cross-sectional study of 518 subjects, 316 with and 202 without obstructive sleep apnea (OSA), underwent polysomnography and completed standardized forms to provide data on personal and familial medical history. Of the patients without OSA, 4% had central sleep apnea, 2% had...
a behavioral sleep disorder, 1% suffered obesity hypoventilation syndrome, and 93% had primary snoring or no other sleep disorder.

Similar to previous investigations, the authors found a strong association between OSA and coronary artery disease (CAD). Both groups had a family history of CAD (61% and 64% of those with and without OSA, respectively), and of cardiovascular disease in general (83% and 84% of those with and without OSA, respectively). However, subjects with OSA were more likely to have a family history of premature CAD mortality (12% vs. 6% of those with and without OSA, respectively; p<0.05).

This study revealed that individuals with OSA are twice as likely to have a family history of premature CAD mortality as those without OSA, suggesting that individuals with OSA have an independently increased risk of CAD. These findings shed more light onto a familiar topic in the US. As an increasing number of individuals are being diagnosed with OSA, research into this disorder is important to improve our knowledge of this growing problem.

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

Endeshaw Y.

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

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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Changes in dreaming induced by CPAP in severe obstructive sleep apnea syndrome patients

Dreaming is an interesting route with which to assess the frequency and robustness of rapid eye movement (REM) sleep in individuals. Investigations have shown a tenuous relationship between enhanced dream recall and increased obstructive sleep-induced apneas. The present study investigated this relationship further to determine whether the use of continuous positive airway pressure (CPAP) and, by extension, a presumed increase in REM sleep, would enhance or reduce the frequency and quality of dream recall. Polysomnograms, spanning 2 years, were used to examine 20 patients with severe obstructive sleep apnea (OSA). Dream recall decreased during the first months of CPAP use but had recovered 2 years later. Patients with untreated OSA were more likely to have an emotional content to and increased verbiage of their dreams, which decreased after CPAP therapy.

Dreaming has posed a dilemma for clinicians practicing sleep medicine as its presence and/or absence can signify either a worsening or amelioration of obstructive sleep apnea (OSA). Short-term memory impairment induced by OSA could theoretically lead to a decreased recall of dreams, but conversely an increased recall could be a result of repeated arousals, making the sleep apneic aware of the recent dream. The one previous study that utilized polysomnography reported that in patients with OSA successfully treated using continuous positive airway pressure (CPAP), its withdrawal led to increased apneas and higher rates of dream recall [1], supporting the latter theory.

This study aimed to ascertain whether the use of CPAP in patients with severe OSA led to a decreased recall of
dreams. Twenty patients with severe OSA and 17 control patients were assessed at baseline using polysomnograms. Polysomnograms were also performed in patients with OSA during the CPAP titration night as well as 3 months and 2 years after commencing treatment. Although at baseline both groups had similar rates of dream recall and, surprisingly, similar percentages of rapid eye movement (REM) sleep, patients with OSA typically had dreams that were infused with emotional content and were more prominently violent and anxious in nature.

During the first night of CPAP use, patients had an increase in the percentage of REM sleep (p=0.056) and stage III–IV non-REM sleep (p<0.001) compared with baseline. Dream recall decreased to 20% in the first night of CPAP use and to 24% during the third month, increasing to 39% after 2 years of usage. The content of the dreams was altered with CPAP use, with the violent and anxious dreams seen at baseline no longer reported.

Based on this data, the authors postulate that dream recall could be related to sleep fragmentation, as previously theorized. The vividly violent and anxious dreams observed at baseline could be the result of the alterations of repetitive oxygen desaturations inducing a hyperactivation of the limbic system and, hence, the emotive contents of the dream. It is unfortunate that the control group was only examined once during the study since a temporal dispersion of the polysomnography, as was performed with the OSA patients, would have strengthened the results of this investigation.

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.

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.

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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 altitude 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/m². 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 O₂ 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 O₂ and rising PCO₂ 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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Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients
Sergi M, Salerno DE, Rizzi M et al.

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. 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.

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

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-hypopnea 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 questionnaires 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 polysomnographies 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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Olfactory dysfunction in patients with narcolepsy with and without REM sleep behaviour disorder


The authors of this study aimed to determine whether there is a distinction between hyposmia in narcoleptic patients with and without rapid eye movement sleep behavior disorder or if narcolepsy alone is associated with hyposmia.

Early identification of progressive neurodegenerative diseases such as Parkinsonian disorders is essential for proper treatment. Over 1 million Americans suffer from Parkinson’s disease and, as with most diseases, an early diagnosis can lead to more effective treatment and a better quality of life. A high percentage of individuals with idiopathic rapid eye movement sleep behavior disorder (RBD) develop Parkinsonian disorders within 10–30 years of the initial diagnosis; therefore, it is vital to further understand this complex relationship. Previous studies have shown that hyposmia (a reduced ability to detect odors) is associated with Parkinson’s disease. Marked olfactory dysfunction has also been shown in patients with RBD both in those with and those without narcolepsy.

A total of 80 subjects participated in the current study; 20 suffered narcolepsy with associated RBD, 20 had narcolepsy without associated RBD, and 40 were age- and sex-matched healthy controls. Subjects underwent neurological examinations to rule out the presence of Parkinsonian symptoms. Olfactory examination, including threshold, discrimination, and identification testing, was performed on each of the subjects, giving a total Threshold–Discrimination–Identification (TDI) score; higher scores indicate a greater ability to discriminate different odors.

Results showed significantly lower TDI scores in narcolepsy patients without RBD compared with controls. Among these patients, hyposmia was mild in 30%, moderate in 15%, and severe in none. Narcolepsy patients with RBD also showed a significantly lower TDI score when compared with controls. Of this group, 30% had mild, 10% had moderate, and 0% had severe hyposmia. Duration of narcolepsy was not significantly correlated with hyposmia, but in patients with narcolepsy and associated RBD, duration of RBD was significantly correlated with impaired olfactory threshold.

These results indicate that, regardless of the presence of RBD, narcolepsy is associated with olfactory dysfunction. Uncovering the links between neurodegenerative disorders and olfactory dysfunction may help further our understanding of the pathophysiology of Parkinsonian disorders.

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Narcolepsy without cataplexy: 2 subtypes based on CSF hypocretin-1/orexin-A findings


Although there has been a consistently positive relationship between both cerebrospinal fluid (CSF) hypocretin/orexin and human leukocyte antigen (HLA) typing in those suffering from narcolepsy with cataplexy, this association has not yet been established in those without the cataplectic subtype. The present study was therefore undertaken to determine this relationship in individuals with narcolepsy without cataplexy. Seventeen patients who fulfilled the diagnostic criteria underwent HLA typing, lumbar punctures to determine CSF hypocretin-1 levels, and multiple sleep latency tests. The results revealed that some narcoleptic patients without cataplexy had low CSF hypocretin-1 levels, and that these levels could be an identifying marker for this subset of patients.

The diagnosis of narcolepsy without cataplexy has been somewhat elusive as, usually, the typical signifiers such as a history of cataplexy, human leukocyte antigen (HLA) typing, and hypocretin-1 deficiency, which are so prominent in narcolepsy with cataplexy, are not present. Diagnosis of the former subtype is normally made on the basis of a nocturnal polysomnogram and a subsequent multiple sleep latency test (MSLT) showing ≥2 sleep-onset rapid eye movement (REM) periods and a mean sleep latency of <8 min. The authors of this study aimed to determine whether there is a correlation between cerebrospinal fluid (CSF) hypocretin-1 levels, MSLT findings, HLA typings, and clinical characteristics in narcoleptics without cataplexy.

Seventeen patients, aged 16–50 years, who were clinically and objectively diagnosed with narcolepsy without cataplexy via medical history, nocturnal polysomnography, and MSLT, were enrolled in this study and underwent both serological HLA typings as well as lumbar punctures for retrieval of CSF hypocretin-1 levels. These patients were further divided into those with low (<110 pg/mL; low group) and normal (>110 pg/mL; normal group) CSF hypocretin-1 levels, the former group comprising five patients. The age of hypersomnia onset was significantly younger in the low group as was mean REM latency. There were, however, no significant differences between the mean sleep latencies and...
Epworth Sleepiness Scale scores of the two groups. Interestingly, DR2 positivity was found in all of the patients in the low group, whereas only four cases in the normal group showed this relationship.

While a previous study had shown decreased CSF hypocretin-1 levels in fewer than 15% of patients with narcolepsy without cataplexy, this study revealed a significantly higher percentage. The authors postulate that part of this discrepancy could lie in the younger age of the low group (11.8 years±3.4 as opposed to 17.6 years±2.4) who may have presented to this study prior to the onset of cataplexy. They also suggest that mild cataplexy may have been overlooked in this group, leading to a greater percentage of those with the lower CSF hypocretin-1 levels. Nevertheless, given these limitations, the authors conclude that a portion of narcoleptic patients without cataplexy manifest with low CSF hypocretin-1 levels, earlier clinical onset, positive HLA status, and shorter mean REM latency.

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EPIEDEMOLOGY

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

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

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.

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.
**INSOMNIA**

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


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 scales 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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**Characterization of insomnia in patients with essential hypertension**


Few studies have investigated insomnia in patients with essential hypertension. The current investigators aimed to determine if relationships exist between insomnia and various biochemical traits associated with hypertension.

Hypertension has recently received interest as the number of patients with this disease is growing, not only across the US but also in European countries. However, data on patients diagnosed with insomnia and essential hypertension are sparse. In the current study, the authors analyzed several biochemical factors related to hypertension and the relationship these factors have in patients diagnosed with essential hypertension and insomnia.

A total of 432 patients from Poland with essential hypertension participated in the current study. Several variables were analyzed, including duration of hypertension, body mass index (BMI), creatinine levels, left ventricular mass index, and any co-existing disorders. Blood pressure was measured every 15 min during the day and every 20 min during the night. The Athens Insomnia Scale was used to define insomnia (score ≥16) and categorize its severity. The control group was drawn from a large cross-sectional study, and consisted of age-, sex-, and BMI-matched normotensive subjects.

Of 432 hypertensive patients, 207 were classified as having insomnia, and 225 were non-insomniacs. Insomnia was more frequent in patients who had co-existing coronary artery disease or diabetes mellitus than in individuals without these disorders. Patients with hypertension were also more...
likely to report insomnia than controls. Hypertensive patients with insomnia were likely to be older and have a significantly longer known duration of hypertension. No significant differences were found in systolic or diastolic blood pressure between insomniacs and non-insomniacs during the 24-h monitoring. In addition, differences in several other measures did not reach significance, including serum electrolyte, glucose, and creatinine concentrations, and other biochemical parameters. Insomniacs had lower creatinine clearance, which remained significant after being adjusted for age.

The current findings are similar to those of previous investigations, reporting higher rates of insomnia in women and older adults. The results indicate that few biochemical factors are related to insomnia and essential hypertension.

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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.


**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 awareness 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 inertia” 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 circadian rhythms.
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 suprachiasmatic 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
Powell NB, Schechtman KB, Riley RW et al.
Sleep 2007;30:331–42.

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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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, 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, pantoprazole 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 appropriate 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.

Acknowledgements
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References
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.

References

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