REMEDICA

VOLUME 1 NUMBER 4 2008

The International Journal of

SLEEP AND WAKEFULNESS

www.sleepandwakefulness.com

UNIVERSITY OF KENTUCKY

Jointly sponsored by the University of Kentucky Colleges of Medicine and Remedica Medical Education and Publishing.

The University of Kentucky is an equal opportunity university.

Cephalon deliver more

This journal is supported by an educational grant from Cephalon.

The International Journal of Sleep and Wakefulness is supported by an educational grant from Cephalon.

Faculty Disclosures

The following are the financial relationships declared by the journal's Editorial Board:

Alan F Schatzberg, MD: Abbott Laboratories, BrainCells, Inc., Bristol-Myers Squibb, Corcept Therapeutics, Inc., CeNeRx Biopharma Eli Lilly & Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Merck & Co., Inc., Neuronetics, Novartis, Pathway Diagnostics, Pfizer, Inc., PharmaNeuroBoost, Sanofi-Aventis, Sepracor Inc., Somaxon Pharmaceuticals, Inc., Wyeth Pharmaceuticals.

Rafael Pelayo, MD: Sanofi-Aventis, Sepracor Inc., Takeda.

Christopher L Drake, PhD: Cephalon, Sanofi-Aventis, Sepracor, Takeda Pharmaceuticals.

Hadine Joffe, MD: Abbott Laboratories, AstraZeneca Pharmaceuticals, Berlex Laboratories, Eli Lilly & Company, Forest Laboratories, Inc., GlaxoSmithKline, Harvard Medical School 50th Anniversary Scholars in Medicine Award, Harvard Medical School Center of Excellence in Women's Health Fund Award, Harvard Medical School Kaplan Depression Research Fellowship, Janssen Pharmaceuticals, Massachusetts General Hospital Claflin Scholars Award, National Alliance for Research on Schizophrenia and Depression, National Institutes of Health, Organon, Inc., Pfizer, Inc., Pfizer/Society for the Advancement of Women's Health Research Scholars Award, Sanofi-Synthelabo, Inc., Sepracor, Inc., Susan G Komen Breast Cancer Foundation Award, Wyeth-Ayerst Pharmaceuticals.

Ned H Kalin, MD: AstraZeneca, Bristol-Myers Squibb, CeNeRx Biopharma, Corcept Therapeutics, Cowen and Company, LLC, Cyberonics, Cypress Biosciences, Eli Lilly, Elsevier, Forest Laboratories, General Electric Corp, GlaxoSmithKline, Janssen Pharmaceuticals, Johnson and Johnson, Neurocrine Biosciences, Neuronetics, Novartis, Promoter Neurosciences, LLC, Sanofi-Synthelabo, Skyland Trail, Wyeth Research.

Andrew Krystal, MD: AstraZeneca, Cephalon, Eli Lilly, Evotec, GlaxoSmithKline, Johnson & Johnson, King Pharmaceuticals, Merck and Co., Inc., National Institutes of Health, Neurocrine Biosciences, Neurogen, Neuronetics, Novartis, Organon, Pfizer, Research Triangle Institute, Respironics, Sanofi-Aventis, Sepracor, Sleep Medicine Education Institute.

David J Kupfer, MD: No relevant financial interests to disclose.

Wallace B Mendelson, MD: Neurocrine, Neurogen, Sanofi-Aventis, Sepracor, Inc., Takeda Pharmaceuticals, VivoMetrics.

Pedram Navab, DO: Cephalon, Jazz Pharmaceuticals.

Thomas Roth, PhD: Abbott, Acadia, Acoglix, Actelion, Alchemers, Alza, Ancil, Arena, AstraZenca, Aventis, Bristol-Myers Squibb, Cephalon, Cypress, Dove, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Jazz Pharmaceuticals, Johnson & Johnson, King Pharmaceuticals, Lundbeck, McNeil, MediciNova, Merck, Neurim, Neurocrine Biosciences, Neurogen, Novartis, Orexo, Organon, Prestwick, Procter & Gamble, Pfizer, Inc., Purdue, Resteva, Roche, Sanofi-Aventis, Schering Plough, Sepracor, Inc., Servier, Shire, Somaxon, Syrex, Takeda Pharmaceuticals, TransOral Pharmaceuticals, Inc., Vanda, VivoMetrics, Wyeth, Xenoport, Yamanuchi.

John W Winkelman, MD: Boehringer Ingelheim, Cephalon, GlaxoSmithKline, Novartis, Pfizer, Sanofi-Aventis, Schwartz Pharma, Sepracor, Takeda Pharmaceuticals.

Phyllis C Zee, MD: Boehringer Ingelheim, GlaxoSmithKline, Jazz Pharmaceuticals, Lippincott-Williams and Wilkins, National Institutes of Health, Neurocrine Biosciences, Northwestern University, Sanofi-Aventis, Takeda Pharmaceuticals, TransOral Pharmaceuticals, Inc.

Editorial Policy

The International Journal of Sleep and Wakefulness is an independent journal published by Remedica Medical Education and Publishing. Editorial control is the sole responsibility of the Editor-in-Chief, Associate Editor, Editorial Advisory Board, and the Editors. Before publication, all material submitted to the journal is subjected to rigorous review by the Editor-in-Chief, Associate Editor, Editorial Advisory Board, Editors, and/or independent reviewers for suitability of scientific content, scientific accuracy, scientific quality, and conflict of interest.

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 for 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.

Publisher's Statement

 The International Journal of Sleep and Wakefulness (1754-307X) is published four times a year. Additional subscription information is available from the publisher.

Remedica Medical Education and Publishing Ltd., Commonwealth House, New Oxford Street, London, WC1A 1NU, UK.
Tel: +44 (0)20 7759 2999 Fax: +44 (0)20 7759 2951
Email: info@remedica.com

Remedica Medical Education and Publishing Inc., 20 N. Wacker Drive, Suite 1642, Chicago, IL 60606, USA.
Tel: +1 (312) 372 4020 Fax: +1 (312) 372 0217.

Editorial Team: Emma Beagley, Jane Bardell Senior Editorial Manager: Scott Millar Publishers: Ian Ackland-Snow, Simon Kirsch
Design and Artwork: AS&K Skylight Creative Services

1754-307X

Contents

LEADING ARTICLE

Excessive Sleepiness: Determinants, Outcomes, and Context

Marcella Oonk, BSc, Adrienne M Tucker, MS, Gregory Belenky, MD, and Hans PA Van Dongen, PhD

Sleep and Performance Research Center, Washington State University, Spokane, WA, USA

Sleepiness level is determined by two interacting neurobiological processes: the homeostatic balance between sleep and wakefulness, and the endogenous circadian rhythm. Disruptions of these two processes contribute to excessive sleepiness in a variety of sleep disorders (e.g. insomnia, shift-work disorder) and in operational settings involving extended hours and shift work. However, excessive sleepiness manifests itself in diverse ways depending upon which variables are measured and how. Broadly, sleepiness measures can be categorized as subjective, physiological, or cognitive performance-related. Aside from a variety of technical measurement issues, different demand characteristics and other context parameters contribute to discrepancies between these categories in measured sleepiness. Diagnosing excessive sleepiness is complicated by the context-dependent diversity in outcomes and by the intertwined contributions of the underlying neurobiological processes. Therefore, for successful diagnosis and treatment of excessive sleepiness it is essential to consider the metrics used to assess it, the underlying neurobiology, and the context. *Int J Sleep Wakefulness* 2008;**1**(4):141–7.

Neurobiological determinants of sleepiness

The International Classification of Sleep Disorders defines daytime sleepiness as "the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep" [1]. This will be adopted here as an operational definition of sleepiness, recognizing that there are gradations of sleepiness level and that sleepiness may occur both day and night. Other terminology is in use for the same general phenomenon, such as drowsiness and tiredness; the term fatigue is typically used in operational environments [2]. There is controversy about the precise interpretation of these concepts and what might differentiate them [3–5]. However, as will be explained, there are multiple dimensions of sleepiness and fatigue, which present more fundamental challenges than mere issues of definition. As such, we will bypass the definition debate, consider the alternative terms to be interchangeable in practice, and use only the term sleepiness here.

Sleepiness is regulated by two basic neurobiological processes: the homeostatic balance between sleep and wakefulness, and the endogenous circadian rhythm [6]. The balance between sleep and wakefulness results in pressure for sleep: the greater the amount of prior wakefulness and/or the smaller the amount of prior sleep, the greater the pressure for sleep. The circadian rhythm opposes the sleep pressure by providing a daytime pressure for wakefulness [7]. Driven by the endogenous biological clock, the wake pressure is greatest in the early evening and lowest in the early morning. During a normal day with daytime wakefulness and nighttime sleep, the two processes counteract each other in such a manner that a stable level of low sleepiness is maintained through most of the day, while a stable level of high sleepiness is maintained through most of the night. This results in alert daytime wakefulness and consolidated nighttime sleep [8].

Alterations in one or both of the two basic regulatory processes lead to increased sleepiness during periods of wakefulness. This can be observed under conditions of sleep deprivation, which disrupt the sleep–wake balance, enhancing the pressure for sleep and thereby the net sleepiness level. It may also be observed when the endogenous circadian rhythm is misaligned relative to the timing of wakefulness, e.g. as tends to occur in shift-work. In this case, the pressure for wakefulness from the circadian rhythm does not oppose the pressure for sleep in a timely fashion, resulting in greater sleepiness during wakefulness and less sleepiness during the sleep period. The latter effect may interfere with the consolidation of sleep, leading additionally to a disruption of the sleep–wake balance and thereby compounding the sleepiness problem.

Address for correspondence: Hans PA Van Dongen, Sleep and Performance Research Center, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495, USA. Email: hvd@wsu.edu

Sleepiness due to sleep disorders

Disruptions of the two basic neurobiological processes regulating sleepiness are involved in a variety of sleep disorders. These disruptions contribute to the excessive sleepiness that is associated with many of them. Therefore, sleep disorders associated with sleepiness can be categorized by the primary neurobiological disruption involved – the sleep–wake balance or the circadian rhythm.

Sleep disorders primarily entailing disruption of the sleep–wake balance include the insomnias, sleep-related movement disorders, and sleep-related breathing disorders. The insomnias are sleep disorders involving repeated difficulty initiating or maintaining sleep or poor quality sleep, usually in association with waking impairment [9]. Sleep-related movement disorders are associated with disturbed sleep and impaired waking function due to movements during sleep [1], in periodic limb movement disorder for instance. Sleep-related breathing disorders, such as obstructive sleep apnea, are characterized by disordered respiration during the sleep period [1], causing sleep disturbance. In these disorders the sleep–wake balance is disrupted in favor of excess wakefulness, causing chronically enhanced sleep pressure leading to sleepiness complaints. In the case of sleep-related breathing disorders, repeated exposure to hypoxia may contribute to waking impairment [10], but the disruption of the sleep–wake balance due to sleep fragmentation also plays a significant role [11].

Sleep disorders primarily entailing disruption of the circadian rhythm are known collectively as circadian rhythm sleep disorders. They are characterized by a misalignment between the timing of the endogenous circadian rhythm and the (desired) sleep time [1]. Examples include the advanced and delayed sleep phase syndromes, irregular sleep–wake rhythm, and shift-work disorder. The misalignment of the circadian rhythm results in improperly timed pressure for wakefulness, such that it is low during wakefulness resulting in enhanced sleepiness, and high during the sleep period resulting in sleep disturbance and disruption of the sleep–wake balance, which further enhances sleepiness.

Mitigating excessive sleepiness is an important goal in the treatment of many sleep disorders. Distinguishing which of the two basic neurobiological processes regulating sleepiness is the primary dysregulated factor is helpful for diagnosis and treatment. However, the causal pathways overlap, which is a problem when trying to differentiate the two processes on the basis of the observed sleepiness alone.

Sleepiness from occupational demands and lifestyle

Sleepiness is not just a symptom of sleep disorders; it is also a by-product of modern lifestyles and the 24/7 economy, which involve demands for wakefulness at all hours of the day and night in large segments of the population [12]. Extended work hours and long commutes leave little time for sleep [13], and shift work schedules interfere with sleeping at the appropriate circadian time [14]. The pathways leading to sleepiness are essentially the same as those described above for sleep disorders, namely disruption of the sleep–wake balance and disruption of the circadian rhythm.

In safety-critical settings sleepiness can have considerable consequences. Sleepiness has been implicated in errors and accidents in the work environment, including catastrophes like the Exxon Valdez grounding and the Chernobyl nuclear meltdown, resulting in monumental cost to society [15]. Conversely, decreasing work demands can help restore sleep–wake balance and circadian alignment, yielding reduced errors and improved work performance [16].

Measuring sleepiness

Sleepiness is expressed in various different ways [17], which can broadly be categorized as subjective, physiological, and cognitive performance related. The measurement of these aspects of sleepiness is discussed in an earlier article in this journal [18]. Here, we recapitulate some of the measurement issues as they relate to difficulties encountered in the diagnosis and treatment of excessive sleepiness.

Subjective sleepiness

The measurement of subjective sleepiness, i.e. the personal awareness of sleepiness, depends on introspection and self-report. Measures of subjective sleepiness include scales and questionnaires of either present feelings of sleepiness (present state) or present and past feelings of sleepiness (sometimes referred to as trait sleepiness [19]). Most subjective sleepiness measures, including the widely used Karolinska Sleepiness Scale [20], inquire about feelings (sensations) of sleepiness. Some measures have been developed to gauge sleepiness by self-report of subjects' behaviors (e.g. falling asleep while watching television), such as the Epworth Sleepiness Scale [21].

Measures of subjective sleepiness provide a convenient way of gathering information on sleepiness, but the sleepiness scores they yield are relative metrics. People vary in how they use subjective scales (e.g. some are more prone to using the extremes of a scale than others). In most cases subjective data can only be interpreted reliably as within-subject change scores, e.g. relative to a person's own baseline data [22]. Inter-individual comparisons are not likely to be meaningful unless averages over large groups are considered.

Furthermore, people may be biased in their personal evaluations of sleepiness and this bias may be affected by

sleepiness itself. The context (i.e. the conditions, circumstances, and social expectations) in which subjective ratings of sleepiness are recorded also affects the outcome [23]. Finally, there are issues of validity, reliability, and other psychometric considerations related to the construction [22] and administration [24] of self-report scales. Nonetheless, self-report measures of sleepiness are important because they aim to capture people's personal experience, which, more so perhaps than objective evidence, is what may prompt them to complain of excessive sleepiness.

Physiological sleepiness

Physiological sleepiness is commonly defined as increased sleep propensity, i.e. a greater tendency to fall asleep [25]. The most widely used measures of sleep propensity are the Multiple Sleep Latency Test (MSLT) [25] and the Maintenance of Wakefulness Test (MWT) [26]. Each of these involves multiple sessions in which a subject is sequestered in a sleep-conducive environment and the time to fall asleep is measured. In the MSLT the subject is asked to try and fall asleep, while in the MWT the instruction is to try and stay awake. The tests are based on the assumption that the more rapidly a person falls asleep, or the more difficult it is to stay awake, the more objectively sleepy he or she must be. The repeated test sessions are performed to help distinguish true physiological sleepiness from extraneous confounders resulting from, for example, motivation or anxiety.

Other physiological measures of sleepiness include the amounts of theta and alpha activity in the waking electroencephalogram (EEG), which are believed to be related to sleepiness [27], and event-related potential measurements derived from the EEG, which exhibit pattern changes in response to sleep deprivation in parallel with sleep propensity [28]. A range of oculomotor measures have been proposed to assess physiological sleepiness, including pupillometry, saccadic velocity, slow eye movements, blinking, and slow eyelid closures [29]. Furthermore, cardiovascular indices have been reported to co-vary with sleepiness [30]. These other physiological measures have been pioneered in operational settings, but are not frequently applied there and are seldom used in clinical practice.

The sleep–wake physiology underlying the various measures of physiological sleepiness is interwoven with other physiological and neurological systems, such as the sympathovagal balance (for EEG-based and cardiovascular measures) or the visual system (for ocular measures). This makes these measures susceptible to internal influences (e.g. mood states) and external influences (e.g. light exposure) that may be hard to control. An additional problem pertaining to the MSLT is that there appear to be people with high sleep ability, i.e. the ability to fall asleep rapidly, without being sleepy [31]. Despite these limitations and the fact that most physiological sleepiness tests are relatively invasive, time consuming, and/or expensive, they are considered useful as objective tools for measuring sleepiness. In fact, the MSLT is seen as the "gold standard" for assessing sleepiness in clinical settings [32].

Cognitive performance impairment

Sleepiness is associated with deficits in a variety of cognitive functions, including sustained attention, working memory, hand–eye coordination, memory retention, decision making, and planning [33]. Various performance tests, ranging from simple reaction-time tests like the widely used Psychomotor Vigilance Test (PVT) [34] to tests that require complex cognitive processing (e.g. the Tower of London test) [35], and even high-fidelity simulators for driving and other real-world tasks, are used to measure these deficits. Typical outcome variables include mean reaction times, number of delayed responses (lapses), number of correct responses, and number of errors.

Problems with performance measures of sleepiness include speed/accuracy trade-offs, practice effects, and vulnerability to internal and external influences, such as motivation, aptitude, environmental stimulation, and test characteristics [23]. Cognitive performance outcomes relying on executive functions – the cognitive abilities needed to set goals and flexibly direct behavior to achieve them – may be the most difficult to interpret. Although they are believed to be particularly affected by sleepiness [36], they are comprised of both simple and complex cognitive components that typically cannot be separated [37]. In addition, measures of complex cognitive performance may be confounded by uncontrollable variability in performance strategies and a variety of other psychometric issues [38].

Regardless of such methodological considerations, it could be argued that measures of cognitive performance deficits associated with sleepiness are valuable because they may have direct relevance to functioning in operational environments. Simple reaction-time tasks requiring sustained attention, including the PVT, have been found to be practical and sensitive performance assays of sleepiness in the laboratory as well as in the field [34,39].

Discrepancies among measures of sleepiness and the role of context

The scientific literature contains numerous reports concerning discrepancies among the various subjective, physiological, and performance-related measures of sleepiness [40–44]. Recent studies of inter-individual differences in the effects of sleep deprivation on sleepiness level have revealed that individuals ranking highest or lowest

on subjective measures of sleepiness do not necessarily rank the same way on physiological [45] or performance-based measures [46]. Within the same person the manifestations of sleepiness can be varied and the correlations among different types of sleepiness measures tend to be low (Fig. 1, top panels). Moreover, sleepiness outcomes are not mirrored in the physiology of sleep itself (Fig. 1, bottom panels), suggesting that sleep–wake neurobiological processes may not be the only determinants of sleepiness.

The discrepancies among measures of sleepiness can partly be explained by the demand characteristics associated with the different measurement tools. Each type of measure requires distinct actions from the individuals being tested. They may, for example, be asked to introspect, try to fall asleep, sit still for artifact-free EEG recording, sustain attention to perform a cognitive task, or drive a driving simulator. Thus, the demand characteristics associated with each measure – the context – constitute an influential differentiating factor. Therefore, what is being asked of people in order to measure their sleepiness co-determines what the outcome will be. Hence, it is important to consider which measure (or suite of measures) of sleepiness is the most relevant for any given situation.

Diagnosing excessive sleepiness

Excessive sleepiness may be defined as "inappropriate or undesired sleepiness that occurs when an individual would be expected to be awake and alert" [47]. Excessive sleepiness involves difficulty maintaining desired wakefulness and adversely affects functioning. Proper diagnosis [48] and treatment [49,50] of excessive sleepiness is challenging due to complexities associated with the basic neurobiological determinants of sleepiness and the different outcome measures of sleepiness (Fig. 2).

Diagnosing patients who report excessive sleepiness is complicated because the sleepiness may present itself in diverse ways, depending on the outcome variable. Rather than selecting one particular sleepiness measure and declaring it a (clinical) standard [1,32], it may be useful to consider the context that matters most to the patient. For instance, when a patient presents to a physician because of difficulty sustaining attention, performance tests assessing this ability could be employed to evaluate the sleepiness level. If a person's ability to drive safely is questioned, the MWT may be a reasonable method to assess excessive sleepiness as it requires staying awake in an environment with low levels of stimulation, which is a critical component of driving ability [51]. If the primary complaint is focused on the sensation of excessive sleepiness, then perhaps the diagnosis should be focused on that subjective concern.

In practice, it may not be possible to pinpoint one specific sleepiness concern and use of a suite of distinct sleepiness measures may be warranted. For instance, one could compose a battery of tests with an assessment of sustained attention (e.g. the PVT), a test of working memory (e.g. the Digit–Symbol Substitution Test [52]), a test of executive function (e.g. the Stroop Color and Word Test [53]), and a subjective measure of sleepiness (e.g. the Epworth Sleepiness Scale [21]). As discussed above, it is possible to obtain seemingly incongruent results from such a mixed test battery. However, when the findings are interpreted in their appropriate contexts, together they can help to determine specific sleepiness vulnerabilities. For example, if an individual were to exhibit considerable impairment only on the PVT this would indicate a sleepiness problem related primarily to sustained attention. It would suggest he or she is most at risk in circumstances highly dependent on sustaining attention, such as driving a car.

When diagnosing excessive sleepiness one should also differentiate which of the underlying neurobiological determinants is primarily involved, the sleep–wake balance or the circadian rhythm [54]. However, sleepiness reflects the influence of the neurobiological determinants in an irrevocably intertwined manner. To disentangle the two processes contextual information is needed, including a sleep–wake history and an assessment of the circadian rhythm [55].

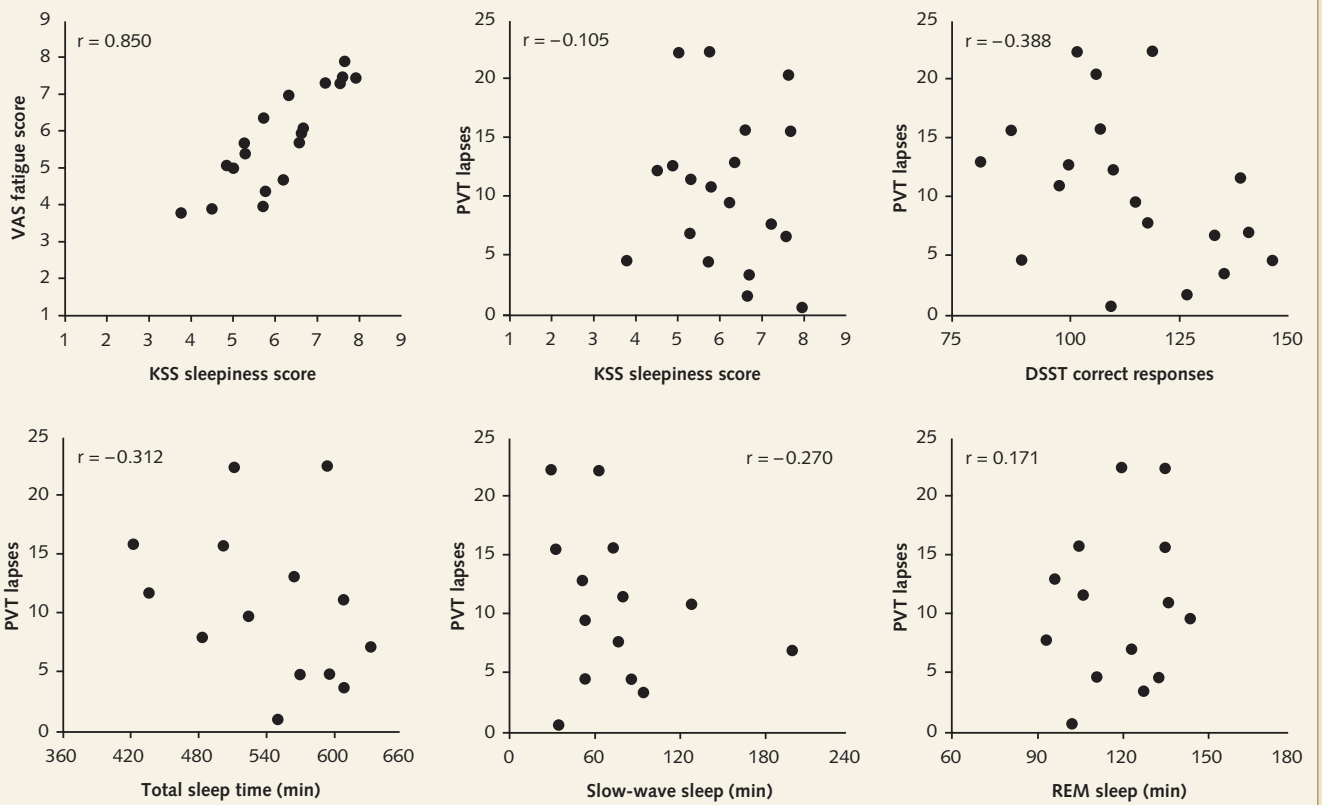
Treating excessive sleepiness

Prescriptive strategies have been established for the treatment of excessive sleepiness resulting from sleep disorders [1]. No such standardization has been implemented for sleepiness countermeasures in the work place and in daily life. However, effective treatment is possible [56]. For excessive sleepiness resulting from disruption of the circadian rhythm, treatment with melatonin or bright light may be useful [57]. For excessive sleepiness resulting primarily from disrupted sleep–wake balance, treatment with hypnotics to increase sleep duration [58] or with stimulants to counteract sleepiness during the waking period [59] may yield improvement. These approaches should typically be complemented with sleep hygiene education and a discussion of the specific sleepiness vulnerabilities and the contexts in which the patient may be at risk.

Treatment options for excessive sleepiness are discussed in the scientific literature [1,49,50,54]. To choose between options a consideration of the context may again be important. For example, the use of hypnotics is restricted in many round-the-clock operational settings because of the potential difficulty waking up to respond to an emergency. However, hypnotics may be useful to improve sleep–wake balance at home.

Excessive sleepiness is often combated by means of stimulants, with caffeine being the most widely used. Large inter-individual differences in sensitivity to caffeine limit the

Figure 1. Different manifestations of sleepiness in relation to each other and to baseline sleep physiology. Sleepiness was induced by keeping subjects awake for 36 h in a controlled laboratory environment [66]. Nineteen healthy adult subjects were twice subjected to this intervention. Their sleepiness levels were measured every 2 h by subjective assessments on the KSS [20] and a VAS of fatigue [46]; by lapses (reaction times ≥500 ms) on the PVT [34]; and by correct responses on a computerized DSST [46]. Data were averaged over the last 24 h of each 36-h sleep deprivation. In light of the trait-like nature of responses to sleep deprivation [46], the data were further reduced by averaging across the two sleep deprivations. The top panels show pair-wise relationships between the different sleepiness measures. For instance, the top left panel compares sleepiness scores on the KSS with those on the VAS; every dot represents a different subject. The correlation among these two variables – both being subjective measures of sleepiness – was high (see the r statistic in the upper left corner). However, as seen in the middle and right panels of this row, much lower correlations were found between the KSS and the PVT, and between the PVT and the DSST [46]. Thus, the overall expression of sleepiness varied considerably from one measure to another. This variability was not predicted by subjects' baseline sleep characteristics (recorded nocturnally at 12 h time in bed [66]), as illustrated in the bottom panels for the PVT (14 subjects).

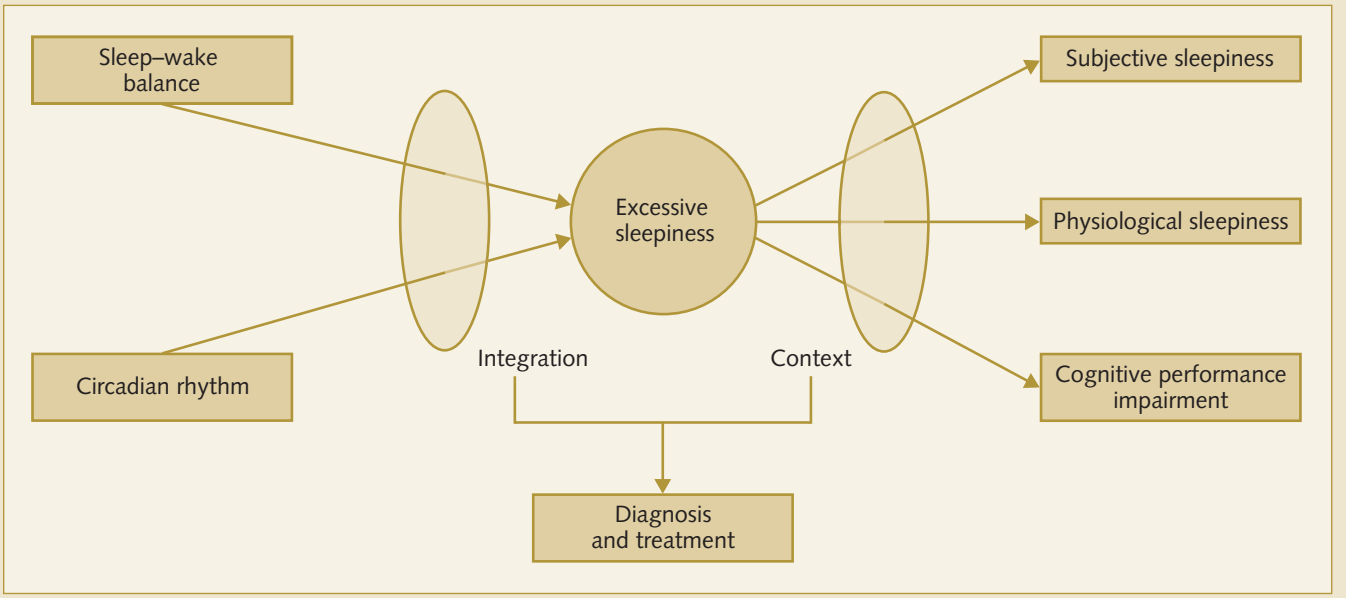


DSST: Digit–Symbol Substitution Task; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor Vigilance Test; REM: rapid eye movement; VAS: Visual Analogue Scale.

usefulness of this countermeasure for some [60]. In addition, different stimulants may affect different aspects of sleepiness to varying degrees. While scientific knowledge in this area is incomplete, preliminary evidence suggests that stimulants may vary in the extent to which they can restore executive functions [61]. Furthermore, stimulants may or may not resolve any mood disturbances associated with excessive sleepiness. Future studies may yield more insight into the need to select specific stimulants depending on the nature of the sleepiness complaint.

To treat excessive sleepiness accompanying shift-work disorder the schedule IV drug modafinil may be prescribed [62]. An intriguing new approach to treating shift-work disorder is to try and improve daytime sleep using melatonin or melatonin analogues, which helps to restore sleep–wake balance and may consequently reduce sleepiness [63]. Recent discoveries regarding the genetics underlying specific vulnerabilities to sleepiness [64,65] will promote the development of more precisely targeted pharmacological countermeasures for different aspects of excessive sleepiness.

Figure 2. Conceptual framework for the underlying neurobiological pathways and the different manifestations of excessive sleepiness. Sleepiness is regulated by processes governing sleep–wake balance and circadian rhythm. Disruptions of these processes have an integrated effect, making it difficult to derive which process is the primary determinant of observed sleepiness. Furthermore, sleepiness manifests itself in different ways, as influenced in part by the context in which it is experienced or measured. These issues complicate the diagnosis and treatment of excessive sleepiness.



Conclusion

Considering excessive sleepiness and its manifestations in the proper context is important for accurate diagnosis and effective treatment. It is helpful to distinguish whether the sleepiness results primarily from disruption of the circadian rhythm or from disruption of the sleep–wake balance. Within a given individual, excessive sleepiness may be expressed to varying degrees depending on which aspect of sleepiness is considered (subjective, physiological, or performance-based). The way sleepiness is manifested depends on the context in which it is experienced, including how it is measured. Similarly, the success of a given treatment approach depends on the context in which it is experienced or evaluated. As such, diagnosis and treatment of excessive sleepiness are not to be seen as routine procedures, but as context-dependent processes requiring interaction with the affected individual, as well as access to a variety of diagnostic tools and treatment options.

Acknowledgments

This work was supported by U.S. Army Medical Research and Materiel Command award W81XWH-05-1-0099, and in part by National Institutes of Health grants HL70154 and RR00040.

Disclosures

The authors have no relevant financial interests to disclose.

References

1. Sateia MJ, editor. *The International Classification of Sleep Disorders* (2nd edition). American Academy of Sleep Medicine, Westchester, IL;2005.
2. Dawson D, McCulloch K. Managing fatigue: it's about sleep. *Sleep Med Rev* 2005;**9**:365–80.
3. Hossain JL, Ahmad P, Reinish LW et al. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Res* 2005;**14**:245–53.
4. Partinen M, Hublin C. Epidemiology of sleep disorders. In: *Principles and Practice of Sleep Medicine*. Kryger MH, Roth T, Dement WC, editors. Elsevier, Philadelphia, PA;2005:626–47.
5. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 2006;**10**:63–76.
6. Borbély AA. A two process model of sleep regulation. *Human Neurobiol* 1982;**1**:195–204.
7. Edgar DM, Dement WC, Fuller CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 1993;**13**:1065–79.
8. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 1994;**166**:63–8.
9. Stepanski EJ. Causes of insomnia. In: *Sleep. A Comprehensive Handbook.* Lee-Chiong T, editor. John Wiley & Sons, Hoboken, NJ;2006:99–102.
10. Punjabi NM, O'Hearn DJ, Neubauer DN, et al. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. *Am J Respir Crit Care Med* 1999;**159**:1703–9.
11. Stepanski EJ. The effect of sleep fragmentation on daytime function. *Sleep* 2002;**25**:268–76.
12. Mallis MM, Brandt SL, Rosekind MR. The challenges of modern day work schedules: effects on alertness, performance, safety, and health. *Int J Sleep Wakefulness* 2007;**1**:2–8.
13. Basner M, Fomberstein KM, Razavi FM et al. American time use survey: sleep time and its relationships to waking activities. *Sleep* 2007;**30**:1085–95.
14. Åkerstedt T. Shift work and disturbed sleep–wakefulness. *Occup Med* 2003;**53**:89–94.
15. Leger D. The costs of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep* 1994;**17**:84–93.
16. Lockley SW, Cronin JW, Evans EE et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med* 2004;**351**:1829–37.
17. Mysliwiec V, Henderson JH, Strollo PJ. Epidemiology, consequences, and evaluation of excessive daytime sleepiness. In: *Sleep Medicine*. Lee-Chiong TL, Sateia MJ, Carskadon MA, editors. Hanley & Belfus, Philadelphia, PA;2002:187–92.

18. Singh M. Conceptualizations of sleepiness and the measurement of hypersomnia. *Int J Sleep Wakefulness Prim Care* 2007;**1**:106–11.
19. De Valck E, Cluydts R. Sleepiness as a state-trait phenomenon, comprising both a sleep drive and a wake drive. *Med Hypotheses* 2003;**60**:509–12.
20. Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990;**52**:29–37.
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;**14**:540–5.
22. Annet J. Subjective rating scales: science or art? *Ergonomics* 2002;**45**:966–87.
23. Van Dongen HPA, Dinges DF. Circadian rhythms in sleepiness, alertness, and performance. In: *Principles and Practice of Sleep Medicine.* Kryger MH, Roth T, Dement WC, editors. Elsevier, Philadelphia, PA;2005:435–43.
24. Yang CM, Lin FW, Spielman AJ. A standard procedure enhances the correlation between subjective and objective measures of sleepiness. *Sleep* 2004;**27**:329–32.
25. Carskadon MA, Dement WC. The Multiple Sleep Latency Test: what does it measure? *Sleep* 1982;**5**(Suppl 2):67–72.
26. Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 1982;**53**:658–61.
27. Bjerner B. Alpha depression and lowered pulse rate during delayed actions in a serial reaction test. *Acta Physiol Scand* 1949;**19**(Suppl 65):1–93.
28. Stolz G, Aschoff JC, Born J et al. VEP, physiological and psychological circadian variations in humans. *J Neurol* 1988;**235**:308–13.
29. Rowland LM, Thomas ML, Thorne DR et al. Oculomotor responses during partial and total sleep deprivation. *Aviat Space Environ Med* 2005;**76**:C104–13.
30. Holmes AL, Burgess HJ, Dawson D. Effects of sleep pressure on endogenous cardiac autonomic activity and body temperature. *J Appl Physiol* 2002;**92**:2578–84.
31. Harrison Y, Horne JA. "High sleepability without sleepiness". The ability to fall asleep rapidly without other signs of sleepiness. *Neurophysiol Clin* 1996;**26**:15–20.
32. Thorpy MJ. The clinical use of the Multiple Sleep Latency Test. *Sleep* 1992;**15**:268–76.
33. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2005;**25**:117–29.
34. Dorrian J, Rogers NL, Dinges DF. Psychomotor vigilance performance: neurocognitive assay sensitive to sleep loss. In: *Sleep Deprivation. Clinical Issues, Pharmacology, and Sleep Loss Effects*. Kushida CA, editor. Marcel Dekker, New York, NY;2005:39–70.
35. Shallice T. Specific impairments of planning. *Philos Trans R Soc London B* 1982;**298**:199–209.
36. Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl* 2000;**6**:236–49.
37. Jonides J, Nee DE. Assessing dysfunction using refined cognitive methods. *Schizophr Bull* 2005;**31**:823–9.
38. Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Med Rev* 2001;**5**:463–75.
39. Balkin TJ, Bliese PD, Belenky G et al. Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *J Sleep Res* 2004;**13**:219–27.
40. Johns M. Rethinking the assessment of sleepiness. *Sleep Med Rev* 1998;**2**:3–15.
41. Olson LG, Cole MF, Ambrogetti A. Correlations among Epworth Sleepiness Scale scores, multiple sleep latency tests and psychological symptoms. *J Sleep Res* 1998;**7**:248–53.
42. Curcio G, Casagrande M, Bertini M. Sleepiness: evaluating and quantifying methods. *Int J Psychophysiol* 2001;**41**:251–63.
43. Danker-Hopfe H, Kraemer S, Dorn H et al. Time-of-day variations in different measures of sleepiness (MSLT, pupillography, and SSS) and their interrelations. *Psychophysiol* 2001;**38**:828–35.
44. Varkevisser M, Van Dongen HPA, Van Amsterdam JGC et al. Chronic insomnia and daytime functioning: an ambulatory assessment. *Behav Sleep Med* 2007;**5**:279–96.
45. Leproult R, Colecchia EF, Berardi AM et al. Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *Am J Physiol Regul Integr Comp Physiol* 2003;**284**:R280–90.
46. Van Dongen HPA, Baynard MD, Maislin G et al. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;**27**:423–33.
47. Wise MS. Objective measures of sleepiness and wakefulness: application to the real world? *J Clin Neurophysiol* 2006;**23**:39–49.
48. Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practicing neurologist. *Brain* 2001;**124**:1482–91.
49. Banerjee D, Vitiello MV, Grunstein RR. Pharmacotherapy for excessive daytime sleepiness. *Sleep Med Rev* 2004;**8**:339–54.
50. Millman RP, Working Group on Sleepiness in Adolescents/Young Adults, AAP Committee on Adolescence. Excessive sleepiness in adolescents and young adults: causes, consequences, and treatment strategies. *Pediatrics* 2005;**115**:1774–86.
51. Sagaspe P, Taillard J, Chaumet G et al. Maintenance of wakefulness test as a predictor of driving performance in patients with untreated obstructive sleep apnea. *Sleep* 2007;**30**:327–30.
52. Wechsler D. *Wechsler Adult Intelligence Scale – Revised*. Psychological Corp., New York, NY;1981.
53. Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Stoelting, Chicago, IL;1978.
54. Hirshkowitz M. Therapy for excessive sleepiness. In: *Sleep. A Comprehensive Handbook*. Lee-Chiong T, editor. John Wiley & Sons, Hoboken, NJ;2006:191–6.
55. Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. *J Biol Rhythms* 1999;**14**:227–36.
56. Rosekind MR, Gander PH, Gregory KB et al. Managing fatigue in operational settings 1: physiological considerations and countermeasures. *Hosp Top* 1997;**75**:23–30.
57. Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. *Ann Clin Biochem* 2006;**43**:344–53.
58. Roehrs T, Roth T. Hypnotics: an update. *Current Neurol Neurosci Rep* 2003;**3**:181–4.
59. Bonnet MH, Balkin TJ, Dinges DF et al. The use of stimulants to modify performance during sleep loss: a review by the Sleep Deprivation and Stimulant Task Force of the American Academy of Sleep Medicine. *Sleep* 2005;**28**:1163–87.
60. Goldstein A, Warren R, Kaizer S. Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine-induced wakefulness. *J Pharmacol Exp Ther* 1965;**149**:156–9.
61. Wesensten NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res* 2005;**14**:255–66.
62. Czeisler CA, Walsh JK, Roth T et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005;**353**:476–86.
63. Wesensten NJ, Balkin TJ, Reichardt RM et al. Daytime sleep and performance following a zolpidem and melatonin cocktail. *Sleep* 2005;**18**:93–103.
64. Rétey JV, Adam M, Gottselig JM et al. Adenosinergic mechanisms contribute to individual differences in sleep deprivation-induced changes in neurobehavioral function and brain rhythmic activity. *J Neurosci* 2006;**26**:10472–9.
65. Viola AU, Archer SN, James LM et al. PER3 polymorphism predicts sleep structure and waking performance. *Curr Biol* 2007;**17**:613–8.
66. Tucker AM, Dinges DF, Van Dongen HPA. Trait interindividual differences in the sleep physiology of healthy young adults. *J Sleep Res* 2007;**16**:170–80.

Awakening to Change: Changes and Implications of Scoring Guidelines

Terri Quinonez, RPSGT, REEGT

Stanford Sleep Disorders Clinic, Stanford, CA, USA

LEADING ARTICLE

The new American Academy of Sleep Medicine (AASM) sleep scoring guidelines have been developed in an attempt to provide consistency amongst all sleep clinical and research centers. This article provides a summary of the progression of sleep scoring, offering a historical perspective of the interpretation of sleep scoring from its beginnings to the present day. The changes brought about by the new AASM guidelines will require the retraining of sleep technologists, as well as the reformatting of reports and sleep analysis software. This review is intended to provide practical implications and advice for these new guidelines, and the differences have been tabulated for easy reference. *Int J Sleep Wakefulness* 2008;**1**(4):148–55.

The field of sleep medicine is undergoing a colossal and critical step in its evolution. The American Academy of Sleep Medicine (AASM) publication, *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications* [1], released in April 2007, has been developed to standardize sleep scoring. The production of this manual was a massive undertaking as it is the first major revision of the classic scoring standards published by Rechtschaffen and Kales in 1968 [2]. AASM-accredited sleep centers and laboratories must comply with the new requirements by July 2008, and many additional facilities also wish to implement the new rules.

The new standardized methodology for the scoring of sleep and related events in adults and children covers technical specifications, recording methods, and data interpretation. It serves to eliminate variability in the interpretation of data from one laboratory to another.

Change in any growing medical field tends to provoke debate, and the new scoring rules are no exception. For many years laboratories have followed the guidelines established by their medical directors, and data interpretation has varied greatly between facilities. At SLEEP 2007, the 21st Annual Meeting of the Associated Professional Sleep Societies, numerous arguments and opinions were expressed about the new scoring manual [3]. There were those who argued that the changes made to the existing scoring criteria were primarily based on consensus rather than actual evidence, and who felt that the manual should therefore be abandoned, while on the other hand were those satisfied with the existing criteria of the AASM manual and thought it needed no changes. Despite these differing views, overall, the field welcomes the new manual. It is a foundation and starting point for the incorporation of current and best available evidence from sleep research and clinical practice into a single resource. Even the founding committee of the manual note that it should not be a static doctrine, but a "living" document that incorporates new information as it becomes available.

As with the new AASM scoring manual, the long-respected Rechtschaffen and Kales manual – the first resource to attempt to define and create rules in the scoring of adult sleep – was subject to controversy. According to a published account, "The rules by Rechtschaffen and Kales present numerous problems; they sometimes even contradict physiological facts. This is due on one hand to the manual being limited to central leads only, and on the other hand to rules which are partly too narrow, partly too broad and partly too complex" [4]. It is fascinating that the authors preferred the switching from central to frontal lead placement to clarify the recognition of certain waveforms. The new scoring manual similarly mentions a procedure listed in the paper, and recommends alternative electrode placement to the frontal lobe.

Early contributors are recognized for their valuable discoveries that moved the field of sleep science forward. As tools able to detect and record activity and related physiological events were developed, sleep became noted as a discipline. Modern researchers have built upon the groundwork of early studies in the field, and with growth comes change. Attempts have been made to categorize

Address for correspondence: Terri Quinonez, Stanford Sleep Medicine Clinic, 211 Quarry Road, Ground Floor N019, Stanford, CA 94305, USA. Email: tquinonez@stanfordmed.org

sleep for the past 75 years. The following section details the developments and milestones leading up to the present day, and highlights the need for a comprehensive, single standardized resource such as the AASM scoring manual in the field of sleep.

Milestones in sleep scoring

The history of the study of sleep is extensive and interesting. The earliest developmental milestone was in 1875, when Caton established methods to characterize the electrical activity of sleep using the recording of brain surface electrical activity in animals [5]. This then takes us to 1913, when Pieron published the first text examining physiological sleep [6]. In the 1920s, Kleitman investigated sleep, wakefulness, and circadian rhythms [7] and in 1929, Hans Berger published findings of the first human electroencephalogram (EEG) recordings [8]. During the 1930s, Tonnie developed the first multichannel ink-writing EEG machine [9], Loomis and colleagues published the first stage classification of non-rapid eye movement (NREM) sleep [10,11,12], and Kleitman published a book on Sleep and Wakefulness [13]. Subsequently, Aserinsky wrote on observations of infants' sleep and eye movements [14,15], and in 1950, Gibbs and Gibbs emphasized age-related differences in sleep onset, separating adult and pediatric sleep [16]. In 1953, Kleitman and Aserinsky described REM during sleep [17], and in the same year, limb myoclonus was detailed [18]. Later that decade, in 1955–8, Dement elucidated on the cyclical nature of nocturnal sleep, sleep stages, and outlined the relationship between REM sleep and dreaming [19]. The first attempt to standardize a scoring system for sleep occurred in 1960, at the inaugural meeting of the Association for the Psychophysiological Study of Sleep (APSS). In 1963, Jouvet identified REM sleep as an independent state of alertness, which he called "paradoxical sleep" [20,21].

The new discipline of "sleep medicine" was broadened by work performed in Europe. Gastaut and colleagues discovered the presence of apnea during sleep in a subgroup of "Pickwickian" patients in 1965 [22]. Respiratory recordings at this time identified periodic interruptions in breathing effort that were both obstructive and non-obstructive. This led to a flood of investigations into the relationship between the "sleeping brain" and the body's vital functions.

Early efforts to characterize the patterns of sleep failed. A study by Monroe conducted in 1967 revealed serious unreliability in the scoring of certain sleep stages [23], and re-emphasized the need for a standardized scoring system. That same year, a special session of the APSS was called. At their 7th annual meeting, the APSS appointed an *ad hoc* committee of investigators to develop terminology and a scoring system that could be used universally by sleep researchers. The committee, under the auspices of the University of California Los Angeles (UCLA) Brain Information Service, met on numerous occasions and corresponded at length during the intervening periods. The group of international investigators from the US, France, Czechoslovakia, and Scotland had considerable experience in scoring sleep records and combined their knowledge to create an enduring standardized scoring manual.

Published in 1968, the result of the committee's work was a proposal entitled *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*, edited by Rechtschaffen and Kales [2]. It was prepared with the expectation that the standardized recording techniques and scoring criteria would be widely used and would increase the comparability of results reported by different investigators. The Rechtschaffen and Kales manual defined techniques, terminology, staging of sleep in normal adults, quantitative sleep summary parameters, EEG characteristics, movement time, and epochs. In the manual's foreword, Rechtschaffen and Kales state: "An evaluation of how much such standardization contributes to reliability of scoring will have to await the development of experience with the system and empirical testing" [2]. Little did they know that their contribution would provide continuity in the staging of sleep for 38 years! The first manual for characterizing normal sleep endured and served countless millions, advancing the science of sleep and the field of sleep medicine.

In 1968, Parmelee catalogued EEG frequencies in infants [24]. In response to the compelling need for a common system for sleep scoring in the infant, *A Manual of Standardized Terminology Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants* was published in 1971, and was devoted to recognizing the qualitative differences of sleep in neonates [25]. Just as in the development of the Rechtschaffen and Kales manual, sleep researchers worldwide came together to form an *ad hoc* committee under the auspices of the UCLA Brain Information Services. The manual was edited by Anders, Emde, and Parmelee, with the aim that the recommended terminology and procedures would be widely used and increase comparability of research results in the field. The Editors hoped it would "be complemented by future manuals dealing with premature and older infants" [25]. Since 1971, several consensus-derived criteria for scoring pediatric sleep have been published. Guilleminault and Souquet described criteria for infants aged 6 weeks to 12 months [26], while the criteria of Hoppenbrouwers et al. were intended for infants from birth to 6 months [27].

Crowell et al. elucidated guidelines for scoring sleep, arousals, and respiratory events in infants aged 35–64 weeks as part of the multicenter CHIME (Collaborative Home Infant Monitoring Evaluation) study [28], and Scholle and Schafer published a consensus-derived age-appropriate adaptation of the Rechtschaffen and Kales criteria for children, which was developed by the Pediatric Task Force of the German Sleep Research Society [29]. In Anders, Emde, and Parmalee's concluding comments it states: "…this handbook should be viewed as working instrument rather than a statute", and goes on to say, "Experience with the manual may suggest possible revisions. When these suggestions accumulate appreciably, it would seem in order to have a review of the manual" [25].

In 1970 the Stanford University Sleep Research Center (Stanford, CA, USA), the first center of its kind, was established by William C Dement. Stanford also introduced the world's first Sleep Disorders Clinic. Sleep disorders are now recognized as a major health concern. In the US there are over 1000 accredited sleep clinics designed to recognize and treat all disorders of sleep, with the total number more than doubling in the past 7 years.

The field of Sleep Medicine has rapidly developed in parallel with the explosion in scientific information and technology. Today, sleep research and sleep medicine comprise many different areas including narcolepsy, sleep and cardiorespiration, studies of pain and sleep, circadian rhythms, shift work and its effects on sleep, sleep deprivation, sleep and aging, infant sleep, parasomnias, and disorders of movement in sleep. Many other professional sleep societies have been formed since the APSS induction in 1960: the American Academy of Sleep Medicine, the Sleep Research Society, the American Association of Sleep Technologists, and the American Academy of Dental Sleep Medicine amongst others.

It has long been recognized that there is little congruity in the scoring of sleep studies among sleep facilities. There have been great advances in our understanding of both adult and pediatric sleep and reconsideration is now necessary to improve the consistency of data and event interpretation. The field of sleep has evolved to a point where a more comprehensive system of standardized measurement is needed; a reliable reference guide that considers events occurring outside normal brain activity. Limitations of the Rechtschaffen and Kales manual included reliance on an epoch-based system with scoring depending on the prior epoch, stage shifts not assigned at the actual time point they occur, difficulty in application to highly fragmented sleep, and single EEG derivation. Some stage boundary rules were hard to follow, there were problems in subjects with no alpha rhythm, and amplitude criteria for slow-wave sleep were arbitrary. Furthermore, age effects, pathological patterns, and digital specifications and analysis were not emphasized in this manual, and definitions of respiratory, leg movements, electrocardiographic data, and arousals were not given.

Recognition of the importance of arousals and their associations with sleep fragmentation, sleep deprivation, and clinical consequences highlighted the need for standardized criteria to score arousals. Since 1968, several groups have attempted to develop rules for scoring, including the Sleep Disorders Atlas Task Force of the American Sleep Disorder Association who, in 1992, defined arousals and movements. [30]. The publication was entitled *EEG Arousals: Scoring Rules and Examples. A Preliminary Report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association*, and it provided consensus rules for scoring arousals. It did not include references or evidence; its purpose was to direct methodology. The title indicated that a more permanent document would follow, and since its publication, the scoring rules have allowed and encouraged significant research. A review of the published data suggested that revisions should be made to the following rules: arousal time window, non-EEG-based arousal events, and cyclic alternating pattern [31,32].

The Siesta group, a worldwide competence center for analyzing sleep and daytime vigilance (wakefulness), also aimed to update the manual by conducting studies of automated methods [33], as the use of digital interfaces requires extensive specifications that were not necessary in the previous scoring manuals.

In 2003, the Board of Directors of the AASM approved the proposed development of a new scoring manual. They hoped it would provide a blueprint for future revisions that would address the needs of the ever-changing field of sleep. It was decided that the proposed rules should be compatible with published evidence, based on biological principles, applicable to clinical disorders, and easily applied by sleep clinicians, scientists, and technologists. The process of developing the new manual was initiated in 2004 and included both a standardized review of the evidence and a standardized method of consensus in order to draft rules, specifications, and terminology that would reflect current scientific evidence and expertise in the field. A task force was formed, comprising more than 60 contributors, including five representatives from software and equipment manufacturers.

Experienced and dedicated members, together with logistical support from the AASM, executed both the evidence review and consensus processes. The new manual would be comprehensive, characterizing sleep throughout the lifespan. It would include areas important to both clinical practice and scientific discovery and would address sleep-

related phenomena not mentioned in previous manuals, specifically arousals, cardiac dysrhythmias, respiratory patterns, movements, and behaviors. It would also incorporate newer technical methods and capabilities.

Four years of careful consideration, decision-making, and the consensus of field specialists were combined to broadly represent the expertise in the field. For more than 2 years, evidence was reviewed by the AASM task forces assigned to each topical area. Principal participants included a supervising steering committee appointed by the AASM Board of Directors, eight task force leaders with content expertise, and eight to 12 task force members, as well as the administrative staff of the AASM.

The process began with task analysis in the following areas: visual, digital, respiratory, pediatric, arousal, cardiac, movements, and geriatric. Evidence in these areas went through topic review and evidence grading looking at precision, reproducibility, consistency, and agreement. RAND consensus, used when clinical trials are not available or are inadequate, was then applied. The RAND/UCLA Appropriateness Method combines the best available scientific evidence with the collective judgment of a panel of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history, and test results. The method was developed in the mid 1980s as part of the RAND Corporation/UCLA Health Services Utilization Study and is applied after literature review. It includes ratings without interaction, panel discussion, and re-rating for consensus. The rationale behind the method is that randomized clinical trials – the "gold standard" for evidence-based medicine – are either generally not available or cannot provide evidence at a level of detail sufficient to apply to the wide range of patients seen in everyday clinical practice. From these results, preliminary rules and specifications were formed that then underwent technical and industry review.

Finally, in April 2007, *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications* was published [1], with the goals of reflecting current knowledge and providing more comprehensive standardized specifications and scoring rules for characterizing natural sleep by polysomnography. Supporting the new manual is a set of seven review articles first published by the AASM in the *Journal of Clinical Sleep Medicine* [34–40]. These seven papers provide underpinnings for the manual and is entitled Review Articles for the AASM Manual for the Scoring of Sleep and Associated Events [34–40].

The development group met their goal of creating a comprehensive scope that incorporates events, technical specifications, and pediatric scoring, as well as modified staging terminology and rules. Arousals, movements, respiratory events, and cardiac events are now combined into the standardized scoring system using both new and existing evidence as well as consensus. Rules were developed to assist in digital analysis. It is not an atlas-based manual but may be complemented by web-based visual examples. The AASM manual is targeted for application in sleep laboratories. Those who compiled the manual recognize that it is not a static doctrine and it will be reviewed on a periodic basis with additions, modifications, and deletions made based on new scientific data. It is intended to become a "living" document that incorporates new information as it becomes available [1].

The changes

The new guidelines and the changes they imply are described below. In addition, a side-by-side comparison of the AASM scoring guidelines with scoring references that were widely used in the past are available online at *www.sleepandwakefulness.com* in the adult, pediatric, and "other" tables of Appendix 1 of this article. Differences are discussed in an additional column.

New technical specifications

The new AASM manual differs from the Rechtschaffen and Kales rules, which were based on and limited to four channels. When the original standards were published, polysomnograms were performed with analogue equipment including ink on paper. Digital technology allows the manipulation of waveforms after collection and lets them to be viewed in different ways, e.g. compressed, expanded, re-referenced, and re-filtered. The technical specifications included in the new manual will provide long-needed consistency among facilities.

The AASM manual includes the following technical specifications: digitalization; minimal and desirable sampling rates, low- and high-frequency filter settings, resolution requirements for computer screens, minimum video card resolution, computer-based sleep analysis, data format, a method of measuring actual individual impedance against a reference and minimal electrode impedances, recommendations for reporting, and computer-supported reports and data file storage considerations. The technical requirements also state that a separate 50–60 Hz filter control should be used for each channel and that recorded video data must be synchronized with the polysomnogram data with an accuracy of at least one video frame per second. These additional changes should ensure consistency in recordings wherever performed and, no matter which software program is utilized, the collected data will meet the same quality standard.

Automated sleep analysis is briefly discussed. The evidence review suggested that computer scoring and quantitative analysis of sleep is still in the formative stage of development [41], and that evidence regarding automated scoring was lacking [42]. The strengths of automated sleep scoring are the automatic removal of artifacts, good quantitative evaluation of delta waves (spectral power and peak analysis), and precision and reliability if the signal quality is good. Unfortunately, some weaknesses still remain in automated scoring. It is difficult to distinguish sleep stage 1 from REM sleep because of similar EEG results (electro-oculography [EOG] is indispensable here), and it is difficult to differentiate between wakefulness and REM sleep as this depends heavily on the quality of the electromyography (EMG) signal.

Technical specifications regarding electrode application

Routine polysomnographic recordings should include:

- Maximum electrode impedances of 5 kΩ (EEG, EOG).
- A minimum digital resolution of 12 bits per sample.

EEG

New EEG montages including frontal derivations, combined with the existing central and occipital derivations, are recommended.

- The recommended derivations are: F4-M1, F3-M2, C4-M1, C3-M2, O2-M1, O1-M2.
- M1 and M2 refer to the left and right mastoid processes, following the 10–20 placement terms.
- To clarify identification of and capture the maximal occurrence of K-complexes and slow-wave activity, the frontal derivations are recommended.
- A minimum of three EEG derivations are required in order to sample activity from the frontal, central, and occipital regions.

EOG

EOG placement has been slightly revised and an alternative recommendation given.

- The recommended EOG derivations are: E1 (LOC)-M2 (E1 is placed directly 1 cm below the left outer canthus). E2 (ROC)-M2 (E2 is placed directly 1 cm above the right outer canthus). In the recommended derivation, the EOG electrodes are no longer placed 1 cm out.

EMG

Not previously defined in the Rechtschaffen and Kales manual [2], the electrode placement for EMG is now clearly defined. Three electrodes are recommended, including one mental and two submental electrodes.

ECG

A single modified lead II placement is recommended for ECG. The recommended electrode placement is one below the right clavicle and the other on the 6th or 7th intercostal space on the left side of the chest.

Scoring of sleep stages

The new manual has very clear guidelines for staging. It incorporates new rules, more detailed definitions, and procedural notes for direct staging. Figures are included in the manual to provide some examples. As the new scoring rules were based on the Rechtschaffen and Kales manual, there is a familiarity to them, easing the transition for scorers.

- Changes in terminology:
  - Wake is now referred to as stage W.
  - The former NREM stages of stage 1, stage 2, stage 3, stage 4 are now identified as N1, N2, and N3 (stage 3 and 4 combined); REM is now labeled stage R.
  - The term delta sleep is now replaced by the term slow-wave sleep.
- The previous "3 minute rule" no longer exists; an adjustment will be noticed in the scoring of N2. N2 sleep can be scored as soon as one or more K-complexes unassociated with arousal or one or more trains of sleep spindle occur in the first half of the epoch or the last half of the previous epoch.
- "Movement time" has been abolished and is no longer a scored event. The new term is "major body movements". These are scored either as stage W if more than 15 s of alpha, 8–12 Hz activity is present for any part of the epoch or if an epoch of stage W precedes or follows the movement, or scored as the same stage as the following epoch.

Scoring of arousals

Many within the sleep field relied on the 1992 publication, *EEG Arousals: Scoring Rules and Examples. A Preliminary Report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association*, for guidance on how to identify and score arousals [30]. It provided criteria to specifically and reliably identify the occurrence of transient arousals for both clinical and theoretical purposes, and determined that an arousal should be scored during any stage of sleep if there is an abrupt shift of EEG frequency, including alpha, theta, and/or frequencies >16 Hz (but not spindles), that last >3 s, with ≥10 s of stable sleep preceding the change [25]. Eleven detailed rules further clarified this definition.

The AASM manual also gives these criteria for scoring arousals during N1, N2, N3 or R:

- An abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that lasts ≥3 s, with ≥10 s of stable sleep preceding the change.

The major difference between the two resources is that the scoring of arousal during REM requires a concurrent increase in submental EMG lasting at least 1 s.

Scoring of respiration

Historically, the area of scoring respiration has proven to be the most inconsistent and controversial. Sleep professionals have been frustrated by the numerous definitions of, and guidelines for, the scoring of respiratory events. Even within individual laboratories, records are returned to scorers for a "rescore". The *Sleep-Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research* [43] was successfully used by many facilities. This document, known as the Chicago Criteria, is a report of an AASM task force and was published in 1999. Its objective was "to develop standard definitions of abnormal breathing events during sleep in adults and their associated syndromes that would facilitate more reliable and accurate reporting in research studies and in clinical practice". Although helpful, it was not universally adopted. With the new AASM manual, specific rules are established for both the adult and pediatric population and details of how to score events such as apnea, hypopnea, respiratory effort-related arousals, hypoventilation, Cheyne Stokes respiration, and periodic breathing are provided. The AASM manual recommends that both the oral–nasal thermal sensor and nasal air pressure transducer should be used for airflow detection, and esophageal manometry or calibrated or uncalibrated inductance plethysmography for detection of respiratory effort.

Cardiac rules

Since it first came into use, technologists have evaluated the ECG channel for normalcy and or cardiac dysrhythmias and added their observations in the comment section of the technical report. With the emergence of the AASM scoring guidelines, we now have clear and consistent guidelines as to what we should be reporting. The manual provides definitions and scoring specifications for sinus tachycardia, bradycardia, asystole, wide complex tachycardia (i.e. ventricular tachycardia and ventricular fibrillation), and narrow complex tachycardias (i.e. atrial fibrillation or atrial flutter with rapid ventricular response, and supra-ventricular tachycardia).

Movement rules

As in other areas, the new scoring manual provides uniformity on movement definitions across sleep facilities. The section provides scoring rules and recommendations for periodic limb movements during sleep (PLMS), bruxism, polysomnographic features of REM behavior disorder, as well as the polysomnographic features of rhythmic movement disorder. Also included are scoring rules for alternating leg muscle activation, hypnagogic foot tremor, and excessive fragmentary myoclonus. The committee decided not to include restless legs syndrome, nocturnal leg cramps, and disorders of partial arousal such as sleep terrors, confusional arousals, and sleep walking.

Scoring PLMS

Until the advent of the new scoring manual, a provisional resource called *The Treatment of Restless Legs Syndrome and Periodic Limb Movement* Disorder [44], a review by the AASM published in 1999, was used by many for scoring PLMS.

The following is a general summary of the scoring of PLMS in the new AASM manual [1]:

- The duration of a limb movement is 0.5–10 s.
- The minimum amplitude is an 8 μV increase in EMG voltage above resting EMG.
- A minimum number of four consecutive LM events is needed to define a PLM series.
- The period length between LMS should be no closer than 5 s and no further apart than 90 s.

Scoring bruxism

The following is a general summary of the scoring of bruxism in the new AASM manual:

- Phasic (transient) elevations are scored as bruxism events when brief increases of chin EMG activity are at least two times the amplitude of background EMG. They are scored if they are 0.25–2 s in duration and if at least three elevations occur in a regular sequence.
- Tonic (sustained) elevations are scored as bruxism if the duration is >2 s.
- Before a new episode of bruxism can be scored, a period of ≥3 s of baseline chin EMG must occur.

Scoring RBD

RBD is scored as either phasic or tonic EMG activity in REM sleep:

- Tonic activity is described as an REM epoch in which ≥50% of the epoch has increased chin EMG amplitude greater than the minimum NREM amplitude. Tonic activity is related to the chin EMG.
- Phasic activity is scored in REM sleep when ≥50% of the epochs contain bursts of EMG activity. The 30 s epoch is divided into 10 mini-epochs, each lasting 3 s in duration. At least five mini-epochs must include bursts. A burst is 0.1–5 s in duration and must be at least four times the amplitude of the baseline EMG signal. Phasic activity is related to the chin or limb EMG.

Scoring rhythmic movement disorder

The following is a general summary of the scoring of rhythmic movement disorder according to the AASM manual:

- Large muscle group EMG is recorded with bipolar surface electrodes.
- Video recording including time synchronization must be included with the polysomnogram.
- A rhythmic burst is two times the baseline EMG amplitude.
- The frequency for scoring rhythmic bursts ranges from 0.5–2.0 Hz.
- There must be four single movements to make a cluster of rhythmic movements.

The future

Future directions will include reliability studies for subjects of different ages and for subjects with sleep disorders. Adaptation of the new rules to digital scoring algorithms will take place. The recommendations will be field-tested and changes proposed. The AASM has posted a list of frequently asked questions on scoring on their website (http://www.aasmnet.org).

Vendors of digital collection and analysis equipment have indicated that their products will be updated to incorporate the new standards by July 2008.

Soon to be gone are the days of inconsistency among sleep facilities. Ambiguity will be put to rest. The field will be going through training and transition as the new guidelines are put into practice by July 2008. Although the new manual has provoked some controversy, it provides much needed standardization. The AASM manual for the scoring of sleep constitutes a major stepping stone towards the development of a single resource that will provide continuity in research and medical practice. The collective efforts of thousands of researchers, educators, students, technologists, and practitioners have culminated in the establishment of sleep medicine. The AASM manual for the scoring of sleep will continue to evolve along with our increasing understanding of the sleep process.

Disclosures

T Quinonez has no relevant financial relationships to disclose.

References

1. Iber C, Ancoli-Israel S, Chesson AL et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Westchester: American Academy of Sleep Medicine, 2007.
2. Rechtschaffen A, Kales A, editors. *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*. NIH Publication No. 204. Washington, Government Printing Office, 1968.
3. Butkov N. Coming to consensus. Addressing practical and technical concerns with the new AASM scoring manual. *Sleep Review* 2008;Jan/Feb:38–42.
4. Kubicki S, Herrmann WM, Höller L et al. Comments on the rules by Rechtschaffen and Kales about the visual scoring of sleep EEG recordings. *EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb* 1982;**13**:51–60 [Article in German].
5. Richard Caton: The electric currents of the brain. *BMJ* 1875;**2**:278.
6. Pieron H. *Le Problème Physiologique du Sommeil*. Masson; Paris; 1913.
7. Kleitman N. A brief history of sleep research. Stanford's Sleep Well. http://www.stanford.edu/~dement/history.html. Last accessed February 3, 1999
8. Berger H. Über das elektroenkephalogramm des menschen. *Arch Psychiatr Nervenkr* 1929;**97**:6–26. [Article in German]
9. Milestones in Neuroscience Research. From www.neurosciences.us/courses/systems/history. Last accessed 1 July 08.
10. Loomis AL, Harvey EN, Hobart G. Potential Rhythms of the cerebral cortex during sleep. *Science* 1935;**81**:597–98.
11. Harvey EN, Loomis AL, Hobart GA. Cerebral states during sleep as studied by human brain potentials. *J Exp Psychol* 1937;**21**:127–144.
12. Loomis AL, Harvey EN, Hobart GA. Electrical potentials of the human brain. *J Exp. Psychol* 1936;**19**:249–79.
13. Kleitman N. *Sleep and Wakefulness*. The University of Chicago Press, Chicago: 1963.
14. Aserinsky E, Kleitman N. Two types of ocular motility occurring in sleep. *J Appl Physiol* 1955;**8**:1–10.
15. Aserinsky E, Kleitman N. Regularly occurring episodes of eye mobility and concomitant phenomena during sleep. *Science* 1953;**118**:273–4.
16. Gibbs EL, Lorimer FM, Gibbs FA. Clinical correlates of exceedingly fast activity in the EEG. *Dis Nerv Syst* 1950;**11**:323–6.
17. Brazier MAB. *A History of Neurophysiology in the 19th Century*, Raven Press, New York: 1988
18. Participation of the cortex in experimental reflex myoclonus. *Electroenceph Clin Neurophysiol* 1953;**5**:177–86.
19. Dement WC. The occurrence of low voltage, fast, electroencephalogram patterns during behavioral sleep in the cat. *Electroenceph Clin Neurophysiol* 1958;**10**:291–6.
20. Jouvet M. Recherche sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. *Arch Ital Biol* 1962;**100**:125–206.
21. Jouvet M. How sleep was dissociated into two states: telencephalic and rhombencephalic sleep? Arch Ital Biol 2004;**142**:317–26.
22. Gastaut H, Tassinari CA, Duron B. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. *Brain Res* 1966;**1**:167–186
23. Monroe LJ. Psychological and physiological differences between good and poor sleepers *J Abnormal Psychol* 1967;**72**:255-64.
24. Parmelee AH, Schulte FJ, Akiyama Y et al. Maturation of EEG activity during sleep in premature infants. *Electroenceph Clin Neurophysiol* 1968;**24**:319–29.
25. Anders T, Emde R, Parmelee A, editors. *A Manual of Standardized Terminology, Techniques and criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants.* Los Angeles: UCLA Brain Information Service, NINDS Neurological Information Network, 1971.
26. Guilleminault C, Souquet M. Sleep states and related pathology. In: Korobkin, R. and Guilleminault, C. (Eds*) Advances in Perinatal Neurology*. Spectrum, New York, 1979:225–47
27. Hoppenbrouwers T. Sleep in infants. In: Guilleminault C (Ed). *Sleep and its disorders in children*. Raven Press, New York. 1987.
28. Crowell DH, Brooks LJ, ColtonT et al. Infant polysomnography: reliability Collaborative Home Infant Monitoring Evaluation (CHIME) Steering committee. *Sleep* 1997;**20**:553–60.
29. Scholle S, Schafer T. Atlas of states of sleep and wakefulness in infants and children *Somnologie* 1999;**3**:163–241.
30. The Sleep Disorders Atlas Task force of the American Sleep Disorders Association. EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task force of the American Sleep Disorders Association. *Sleep* 1992;**15**:173–84.
31. Terzano MG, Parrino L, Boselli M et al. Polysomnographic analysis of arousal response in obstructive sleep apnea syndrome by means of the cyclic alternating pattern. *J Clin Neuropysiol* 1996;**13**:145–55.
32. Bruni O, Rerri R, Miano S et al. Sleep cyclic alternating pattern in normal preschool-aged children. *Sleep* 2005;**28**:220–30.
33. Anderer P, Gruber G, Parapatics S et al. An E-health solution for automatic sleep classification according to Rechtschaffen and Kales: validation study of the Somnolyzer 24 x 7 utilizing the Siesta database. *Neuropsychobiol* 2005;**51**:115–33.

34. Penzel T, Hirshkowitz M, Harsh J. Digital analysis and technical specifications. *J Clin Sleep Med* 2007;**3**:109–20.
35. Silber MH, Ancoli-Israel S, Bonnet MH. The visual scoring of sleep in adults. *J Clin Sleep Med* 2007;**3**:121–31.
36. Bonnet MH, Doghramji K, Roehrs T. The scoring of arousal in sleep: reliability, validity, and alternatives. *J Clin Sleep Med* 2007;**3**:133–45.
37. Caples SM, Rosen CL, Shen WK. The scoring of cardiac events during sleep. *J Clin Sleep Med* 2007;**3**:147–54.
38. Walters AS, Lavigne G, Hening W. The scoring of movements in sleep. *J Clin Sleep Med* 2007;**3**:155–67.
39. Redline S, Budhiraja R, Kapur V. The scoring of respiratory events in sleep: reliability and validity. *J Clin Sleep Med* 2007;**3**:169–200.
40. Grigg-Damberger M, Gozal D, Marcus CL. The visual scoring of sleep and arousal in infants and children. *J Clin Sleep Med* 2007;**3**:201–40.
41. Penzel T, Hirshkowitz M, Harsh J et al. Digital analysis and technical specifications. *J Clin Sleep Med* 2007;**3**:109–20.
42. Mahowald MW. Other Parasomnias. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. 4th ed. Elsevier Saunders, 2005:917–25.
43. The American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;**22**:667–89.
44. Hening W, Earley C, Kushida C et al. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. *Sleep* 1999;**22**:970–99.

Sleep Duration and Cardiovascular Health

Hassan Chami MD, MSc, and Daniel J Gottlieb, MD, MPH

VA Boston Healthcare System and Boston University School of Medicine, Boston, MA, USA.

Voluntary sleep restriction is a common behavior in industrialized societies. Epidemiological studies have revealed that sleep duration is associated with mortality, coronary heart disease, diabetes mellitus, and hypertension. Whether short sleep duration causes cardiovascular disease remains unproven, but it is biologically plausible and supported by experimental studies on sleep restriction. The mechanisms underlying this association remain to be elucidated and may include alterations in the activity of the sympathetic nervous system, renin–angiotensin system, or hypothalamic–pituitary–adrenal axis. While no study has proven that sleep extension reduces cardiovascular risk, the available evidence suggests that sleeping for 7–8 h per night should be recommended as an important component of a healthy lifestyle. *Int J Sleep Wakefulness* 2008;**1**(4):156–65.

Typical daily sleep duration appears to have declined for more than a generation among adults in the US, and probably throughout the industrialized world. Median sleep duration has reportedly fallen from 8 h per night in the 1950s to 7 h per night in the past decade, with more than one-third of adults now claiming that they sleep fewer than 7 h per night [1,2]. While chronic insomnia is common, much of the reduction in sleep duration is voluntary, and nearly half of adults report that they restrict sleep to watch television, use the internet, or work [3]. While the optimum daily sleep duration has not been clearly established, and like any biological parameter is probably subject to considerable inter-individual variation, it appears that most individuals sleeping for <7 h per night are truly sleep-deprived. It was noted 15 years ago that when healthy young adults were given the opportunity to sleep for 14 h per night, their sleep duration initially increased to a mean of 10.6 h per night and then declined gradually to a mean of 8.2 h per night over 4 weeks [4]. Klerman and Dijk have recently expanded on this observation, demonstrating that among 17 healthy young adults who were free of sleep disorders and without complaints of excessive sleepiness, four out of five of the subjects with habitual sleep durations of <8 h per night had pathologically short mean sleep latencies of <5 min [5]. Moreover, when all subjects were given extended time in bed, shorter habitual sleep duration was associated with longer total sleep time, even on the third night of extended time in bed [5]. This and other evidence suggests that, from the standpoint of sleepiness and cognitive function, the optimum sleep duration for most individuals is likely to be at least 8 h per night (see, for example, the excellent study of chronic partial sleep deprivation by Van Dongen et al. [6]).

The extensive literature on the neurobehavioral and cognitive consequences of insufficient sleep provides ample justification for the common medical recommendation that adults should sleep for at least 7–8 h per night. A smaller body of evidence suggests that sleep deprivation may have other important physiological consequences. It was first reported more than 40 years ago that both short and long sleep duration are associated with mortality [1], a finding that has been replicated in subsequent studies [10–12]. A smaller number of observational studies have found associations of both short and long sleep duration with prevalent and incident coronary heart disease, and a growing body of evidence suggests that insufficient sleep may cause manifestations of the metabolic syndrome, including impaired glucose tolerance, diabetes mellitus (DM), hypertension, and obesity [7,8]. If short sleep duration does cause these ills, the potential public health impact of a demographic shift to shorter sleep durations may be very high indeed. While a clear causal effect of short sleep duration on cardiovascular and metabolic disease remains unproven, a growing body of evidence from both observational and experimental studies does support such an inference. A recent article in this journal detailed the relationship between sleep duration and obesity, together with possible mechanisms underlying the association [8]. In this manuscript we review the observational data supporting associations of sleep duration with mortality, coronary heart disease, DM, and hypertension and discuss possible mechanisms underlying the observed association between sleep duration and poor

Address for correspondence: Daniel J Gottlieb, VA Boston Healthcare System, West Roxbury Campus, 1400 VFW Parkway (111PI), West Roxbury, MA 02132, USA. Email: gottlieb@bu.edu

Table 1. Observational studies of the association between sleep duration and mortality.

Study	Country	Participants (n)	Design	Main findings
Kripke et al. [10] 1979 Cancer Prevention Study 1	USA	1 million	Prospective	Over the 6-year follow-up period, RR for mortality: 2.8 for men and 1.48 for women sleeping for <4 h vs. 7 h, 1.8 for men and women sleeping ≥10 h vs. 7 h
Wingard and Beckman [12] 1983 Alameda County, CA	USA	2491 women, 2222 men	Prospective	Increased 9-year mortality risk (RR 1.6) in women not sleeping 7–8 h vs. 7–8 h per night
Pollak et al. [9] 1990	USA	1855	Prospective	Over the 3.5-year follow-up period there was no association between sleep duration and mortality
Kojima et al. [15] 2000 Gifu Prefecture	Japan	5322	Prospective	Over the 12-year follow-up period, RR for mortality: 1.90 for short sleep duration (<7 h) and 1.94 for long (≥10 h) sleep duration vs. 7–8 h in men but not in women
Kripke et al. [11] 2002 Cancer Prevention Study 2	USA	1.1 million	Prospective	Over the 6-year follow-up period, increased adjusted (32 confounders) mortality risk for men and women sleeping for >7 h or <7 h
Amagai et al. [16] 2004 Jichi Medical School cohort	Japan	6906 women 4419 men	Prospective	Over the 8.5-year follow-up period, adjusted HR for mortality: 2.4 (95% CI 1.3–4.2) for men sleeping for <6 h, 1.5 (95% CI 1.0–2.4) for women sleeping for >9 h vs. 7–7.9 h
Patel et al. [13] 2004 Nurses Health Study	USA	82 969 women	Prospective	Adjusted RR of death: 1.15 (95% CI 1.02–1.29) for women sleeping for ≤5 h, 1.01 (95% CI 0.94–1.08) for 6 h, 1.12 (95% CI 1.05–1.20) for 8 h, 1.42 (95% CI 1.27–1.58) for ≥9 h vs. 7 h
Tamakoshi et al. [14] 2004 Japan Collaborative Cohort Study	Japan	60 158 women, 43 852 men	Prospective	Over the 10-year follow-up period, long and short sleep duration increased mortality, but no association between short sleep and mortality in men after adjustment for stress and depression

CI: confidence interval; HR: hazard ratio; RR: relative risk.

health. Finally, we suggest practical guidelines for encouraging patients to obtain adequate sleep.

Association of sleep duration with mortality, cardiovascular disease, and the metabolic syndrome

Association of sleep duration with mortality

Following Hammond's seminal presentation of data from the American Cancer Society's Cancer Prevention Study revealing that self-reported usual sleep durations either shorter or longer than 7 h per night are associated with increased mortality rates [1], this finding has been replicated multiple times [10–12]. While sleep duration did not predict mortality in a cohort of 1855 elderly residents of an urban community over a follow-up period of 3.5 years [9], larger studies including middle-aged and younger adults, with longer follow-up periods, found higher mortality rates associated with both short and long sleep duration (Table 1).

An expanded analysis of the Cancer Prevention Study data, using 6-year follow-up data from 1 million men and women and controlling for age, sex, and history of illness (heart disease, hypertension, DM, and stroke), found that a reported sleep duration of <4 h was associated with increased all-cause mortality [10]. The subsequent Cancer Prevention Study 2, which included 1.1 million men and women aged 30–102 years, found that a sleep duration longer or shorter than 7 h was associated with increased mortality over a 6-year follow-up period in both men and women, after more extensive covariate adjustment for 32 potential confounders, such as smoking, exercise, dietary fat, and insomnia frequency, as well as multiple medical illnesses, including history of heart disease, DM, and hypertension [11]. All-cause mortality over 9 years was also higher in subjects sleeping for ≤6 h or ≥9 h per night compared with those sleeping for 7–8 h, in a random sample of 4713 subjects aged 30–69 years from Alameda County (CA, USA), after adjustment for age, sex, race, socioeconomic status, health status, smoking, physical inactivity, alcohol, weight, use of health services, social networks, and life satisfaction [12]. A similar association was observed among the 82 969 women participating in the Nurses Health Study [13]. After adjusting for age, smoking,

Table 2. Observational studies of the association between sleep duration and coronary heart disease.

Study	Country	Participants (n)	Design	Main findings
Partinen et al. [23] 1982	Finland	5419 men	Cross-sectional	A history of myocardial infarction more common with sleeping for >9 h. Symptomatic coronary heart disease more common with a sleep duration of <6 h
Qureshi et al. [26] 1997 NHANES-I	USA	7844	Prospective	No significant association in the adjusted analysis
Ayas et al. [24] 2003 Nurses Health Study	USA	71 617 women	Prospective	Adjusted RR for a coronary event was 1.45 (95% CI 1.10–1.92) for sleeping for ≤5 h, 1.18 (95% CI 0.98–1.42) for 6 h, 1.38 (95% CI 1.03–1.86) for ≥9 h vs. 8 h
Gottlieb et al. [22] 2006 SHHS	USA	5910	Cross-sectional	Prevalence of cardiovascular disease 23.3%, 14.7% and 21.4% in participants who reported sleeping <8 h, 7–8 h and >9 h respectively (unadjusted)
Meisinger et al. [25] 2007 MONICA Study	Germany	3388 women 3508 men	Prospective	Adjusted HR of MI: 2.98 (95%CI 1.48–6.03) in women sleeping ≤5 h and 1.40 (95% CI 0.74–2.64) in women sleeping ≥9h compared to 8 h sleep. No significant association between sleep duration and incident MI in men

CI: confidence interval; MI: myocardial infarction; MONICA: Monitoring trends and determinants on cardiovascular diseases; NHANES-I: the first National Health and Nutrition Examination Survey; RR: relative risk; SHHS: Sleep Heart Health Study.

alcohol, exercise, depression, snoring, obesity, history of cancer, and cardiovascular disease, the adjusted mortality risk was 1.15 (95% confidence interval [CI] 1.02–1.29) for ≤5 h, 1.01 (95% CI 0.94–1.08) for 6 h, 1.12 (95% CI 1.05–1.20) for 8 h, and 1.42 (95% CI 1.27–1.58) for ≥9 h compared with 7 h of sleep per night [13].

Three studies from Japan have reported similar findings. In the Japan Collaborative Cohort Study of 104 010 adults aged 40–79 years, with a mean follow-up duration of 10 years, a U-shaped relationship between sleep duration and mortality was observed, with the lowest mortality rate associated with 7 h of sleep per night [14]; this association appeared to be stronger in women than men. Two smaller studies from Japan, in which subjects were followed for 8.5–12 years, also showed a U-shaped relationship between sleep duration and mortality, with the lowest mortality rate associated with a sleep duration of 7–8 h per night [15,16]. In these studies, the association between short sleep duration and mortality appeared stronger in men.

Association of sleep duration with coronary heart disease and stroke

Heart disease remains the most common cause of death in the industrialized world. In contrast to the many studies on sleep duration and mortality, few studies have examined the relationship between sleep duration and cardiovascular disease. Studies examining insomnia symptoms have found an increased risk of myocardial infarction (MI) and cardiovascular death associated with difficulty initiating or maintaining sleep in middle-aged [17,18] and older subjects [19,20]; however, patients with insomnia commonly have a normal sleep duration [21].

A small number of studies have specifically addressed the associations of sleep duration with prevalent and incident coronary heart disease (Table 2). In the SHHS (Sleep Heart Health Study), the prevalence of cardiovascular disease at baseline was higher in subjects who reported sleeping for <8 h (23.3%) or >9 h (21.4%) than in those who reported sleeping for 7–8 h per night (14.7%) [22]. In a cross-sectional study of 5419 adult men in Finland, the frequency of reported symptomatic coronary heart disease was higher among those who reported sleeping for <6 h per night, after adjusting for age, sleep quality, sleeping pill and tranquilizer use, smoking, alcohol, type A score, neuroticism, use of cardiovascular drugs, and history of hypertension, while those who reported sleeping for >9 h per night were more likely to have a history of MI [23].

In a prospective analysis of 71 617 middle-aged women from the Nurses Health Study, Ayas et al. reported an increased incidence of coronary events associated with both short (≤5 h) and long (≥9 h) sleep durations, with relative risks of 1.45 (95% CI 1.10–1.92) and 1.38 (1.03–1.86), respectively, compared with a sleep duration of 8 h, over a 10-year follow-up period, after adjusting for shift work, hypercholesterolemia, body mass index (BMI), smoking, snoring, exercise level, alcohol consumption, depression, aspirin use, postmenopausal hormone use, DM, hypertension, and family history of MI [24].

Table 3. Observational studies of the association between sleep duration and diabetes.

Study	Country	Participants (n)	Design	Main findings
Bjorkelund et al. [29] 2005 Gothenburg population study	Sweden	1462 women	Prospective	No association between sleep duration and incidence of diabetes over 32 years of follow-up
Yaggi et al. [30] 2006 Massachusetts Male Aging Study	USA	1139 men	Prospective	Men sleeping for ≤5 h or >8 h vs. 7 h were more likely to develop DM (RR 1.95 [95% CI 0.95–4.01] and 3.12 [95% CI 1.53–6.37]), respectively
Mallon et al. [28] 2005	Sweden	620 women 550 men	Prospective	Sleeping for ≤5 h was associated with an increased adjusted DM risk over 12 years of follow-up in men (RR 2.8, 95% CI 1.1–7.3) but not in women (RR 1.8, 95% CI 0.5–6.8)
Ayas et al. [27] 2003 Nurses Health Study	USA	70 026 women	Prospective	Over the 10-year follow-up period, sleeping for ≤5 h vs. 8 h was associated with an increased adjusted risk of symptomatic DM (RR 1.37, 95% CI 1.07–1.77]) but not total DM (RR 1.18, 95% CI 0.96–1.44]) over 10 years of follow-up. Sleeping for ≥9 h was associated with increased total DM and symptomatic DM (RR 1.29 [95% CI 1.05–1.59] and 1.36 [95% CI 1.04–1.73]), respectively
Gangwisch et al. [31] 2007 NHANES-I	USA	8992	Prospective	Adjusted OR for incident DM: 1.47 (95% CI 1.03–2.09) for ≤5 h, 1.08 (95% CI 0.80–1.47) for 6 h, 1.52 (95% CI 1.06–2.17) for ≥9 h vs. 7 h of sleep

CI: confidence interval; DM: diabetes mellitus; NHANES-I: the first National Health and Nutrition Examination Survey; OR: odds ratio; RR: relative risk.

Compared with a sleep duration of 8 h, a short sleep duration (≤5 h) was also associated with incident MI in women (n=3388, HR 2.98, 95% CI 1.48–6.03) but not in men (n=3508, HR 1.13, 95% CI 0.66–1.92) who participated in the prospective MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) study over a mean follow-up of 10.1 years [25]. The analysis was adjusted for BMI, education, dyslipidemia, alcohol intake, parental history of MI, physical activity, regular smoking, hypertension, history of diabetes, and menopause status [25]. The association was not significant for long sleep time in either men or women.

In 7844 subjects from the NHANES I (the first National Health and Nutrition Examination Survey) cohort, the adjusted risk for coronary heart disease over a 10-year follow-up period was modestly increased in subjects who reported sleeping for <6 h compared with those who were sleeping for 6–8 h per night [26]. The association was of borderline statistical significance, with an odds ratio (OR) of 1.3 (95% CI 1.0–1.8) after adjusting for demographics, education, smoking, BMI, cholesterol, systolic blood pressure (SBP), and DM. The association was not found to be significant for long sleep duration. Conversely, long but not short sleep duration was associated with an increased risk of stroke (OR 1.5, 95% CI 1.1–2.0).

Association of sleep duration with the metabolic syndrome

One possible explanation for the associations of sleep duration with coronary heart disease and mortality is an increase in the prevalence of the metabolic syndrome, including obesity, impaired glucose metabolism, and hypertension. A large number of studies have now documented the strong association between sleep duration and prevalent obesity in both children and adults, and several prospective studies have found sleep duration to predict subsequent weight gain. These findings and proposed mechanisms for the association have recently been reviewed in these pages [8] and elsewhere [7] and will not be re-examined here, other than to note that in adults both short and long sleep duration have usually been found to be associated with obesity, while in young children the association is more often monotonic, with short but not long sleep duration associated with obesity.

A number of observational studies have explored the relationship between sleep duration and DM, including five prospective studies in middle-aged adults, ranging in size from 1139 to 70 026 subjects and in duration of follow-up from 10 to 32 years (Table 3) [27–31]. Three of the five studies found an increased risk of incident DM in both short

Table 4. Observational studies of the association between sleep duration and hypertension.

Study	Country	Participants (n)	Design	Main findings
Gottlieb et al. [22] 2006 SHHS	USA	5910	Cross-sectional	Adjusted OR for HTN: 1.66 (95% CI 1.35–2.04) for sleeping for <6 h, 1.30 (95% CI 1.04–1.62) for ≥9 h vs. 7–8 h
Gangwisch et al. [36] 2006 NHANES-I	USA	4810	Prospective	HR for HTN: 2.10 (95% CI 1.58–2.79) for sleeping for <5 h vs. 7–8 h. Adjusting for potential confounders partially attenuated this relationship
Cappuccio et al. [33] 2007 Whitehall II	UK	5766	Cross-sectional	Adjusted prevalence OR: 2.01 (95% CI 1.13–3.58) for sleeping for ≤5 h vs. 7 h among women but not among men
		3691	Prospective	Higher risk of incident hypertension in women with short sleep, adjusting for age and employment (OR 1.56 [95% CI 1.07–2.27] for sleeping for 6 h, 1.94 [95% CI 1.08–3.50] for ≤5 h vs. 7 h). The association not statistically significant when adjusting for cardiovascular factors and psychiatric conditions
van den Berg et al. [34] 2007 Rotterdam study	The Netherlands	5058	Cross-sectional	No association between sleep duration and hypertension in an elderly population
Bjorvatn et al. [35] 2007 Hordaland Health Study	Norway	8593 men 9983 women	Prospective	Sleep duration not associated with SBP >140 mmHg or DBP >90 mmHg when adjusting for gender, smoking, and BMI, but the authors did not consider anti-HTN medication.

BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HR: hazard ratio; HTN: hypertension; NHANES-I: the first National Health and Nutrition Examination Survey; OR: odds ratio; SBP: systolic blood pressure; SHHS: Sleep Heart Health Study.

and long sleepers [27,30,31] after adjustment for a measure of adiposity (BMI, waist girth, or obesity) and a variety of additional covariates. These studies assessed sleep duration once at the beginning of the follow-up period and used self-report of the diagnosis of DM. Because of changes in sleep duration over time, the observed associations may be lower than the true association of sleep duration with DM. Self-report undoubtedly misses cases of DM identified through objective testing; however, the findings of these prospective studies are similar to the cross-sectional associations of sleep duration with DM and impaired glucose tolerance identified by oral glucose tolerance testing in a subset of the SHHS cohort [32]. The one prospective study that found no association of sleep duration with incident DM had a follow-up period of 32 years, and the potential for large changes in sleep habits over this time (the reported kappa statistic for a sleep duration of <6 h per night was 0.11), competing risk factors for DM in this aging cohort, and the inclusion of long sleepers in the referent group may have biased towards a null result [29].

While the associations of short sleep duration with DM and impaired glucose tolerance have received considerable attention in recent years, there has been comparatively little focus on the association of sleep duration with hypertension, although it has been addressed in several recent observational studies (Table 4). In a cross-sectional analysis of 5910 adults from the community-based SHHS, a self-reported sleep duration above or below 7 h per night was associated with an increased prevalence of hypertension (defined as SBP ≥140 mmHg, diastolic blood pressure [DBP] ≥90 mmHg, or use of anti-hypertensive medication), after adjustment for demographic variables, apnea–hypopnea index, and BMI. The effect was most pronounced in subjects who reported sleeping for <6 h per night (OR 1.66, 95% CI 1.35–2.04) [22]. The association persisted after adjusting for caffeine and alcohol consumption, smoking, insomnia, depression, sleep efficiency, and DM or cardiovascular disease. A cross-sectional analysis from the Whitehall II cohort of 5766 UK civil servants aged 35–55 years, using the same definition for hypertension, concluded that a sleep duration of ≤5 h was associated with a higher prevalence of hypertension compared with a sleep duration of 7 h per night, among women but not men [33]. The analysis was adjusted for age, employment, alcohol, smoking, physical activity, BMI, physical functioning scale of the 36-item Short Form Health Survey, depression, hypnotic use, and use of

drugs for cardiovascular vascular disease. In the community-based Rotterdam study of 5058 elderly subjects aged 58–98 years, sleep duration was not associated with prevalent hypertension, regardless of whether sleep duration was assessed by patient report or actigraphy (performed in a subset of 975 participants) [34]. This study differed from the prior reports in terms of the definition of hypertension (SBP >160 mmHg or DBP >100 mmHg) and the somewhat older age of the participants [34]. Likewise, in a subgroup of 40–45-year-old participants in the cross-sectional Hordaland Health Study, no significant adjusted association of either SBP or DBP with sleep duration was found, although no mention is made of medication use in this sample [35].

Two prospective studies have also addressed the association between sleep duration and hypertension. Analysis of data from NHANES-I (n=4810) revealed that a self-reported sleep duration of ≤5 h per night was associated with an increased incidence of hypertension over a mean follow-up period of 8–10 years. Hypertension was ascertained using physician diagnosis, hospital record, or cause of death. The association was attenuated but remained statistically significant after adjusting for gender, education, daytime sleepiness, depression, physical activity, alcohol, smoking, pulse rate, overweight or obese habitus, and DM. This effect was seen only in those younger than 60 years of age [36]. In contrast, in 3691 normotensive individuals from the Whitehall II cohort, over a mean follow-up duration of 5 years, short sleep duration was associated with a higher risk of hypertension in women when adjusting only for age and employment status, but there was no significant association after adjusting for BMI and the other cardiovascular risk factors and psychiatric conditions noted above [33].

Summary of the data from observational studies

It is clear that self-reported usual sleep duration is significantly associated with mortality after adjusting for many known mortality risk factors. Although sleep times both above and below 7 h per night are significantly associated with mortality in these very large cohorts, it must be acknowledged that the effects are generally modest at sleep durations of 6 h per night. While all of these studies use self-reported sleep duration, typically derived from a single question, self-reported usual sleep duration has been found to correlate highly with 1 week of sleep diaries (r=0.79) [13]. However, some change in sleep duration over the follow-up period is likely. Self-reported sleep duration was found to be only modestly stable over a mean interval of 2.4 years (r=0.57) in the SHHS [32], while in the Gothenburg study the stability of a sleep duration of <6 h per night was low over a 32-year interval (kappa statistic 0.11) [29]. This is expected to result in non-differential misclassification of the exposure and thus bias towards a null result. An association between insomnia symptoms and mortality has been reported, and insomnia sufferers often underestimate their true sleep time [21], potentially biasing studies of the correlates of sleep duration; however, in the Cancer Prevention Study 2, the association between sleep duration and mortality persisted after adjustment for insomnia frequency.

While data for cardiovascular disease, DM, and hypertension are less extensive and, overall, somewhat less consistent than those for mortality, the preponderance of evidence from these studies also supports associations of sleep duration with poor cardiovascular and metabolic health outcomes. The same considerations noted above regarding growing misclassification of exposure to short sleep duration over the follow-up period apply to these conditions. Moreover, if short sleep duration is indeed a cause of obesity, adjustment for obesity may lead to an underestimate of the true effect of sleep duration on health. When it has been included in analyses, insomnia and its possible associated morbidity do not appear to confound these associations.

Obstructive sleep apnea (OSA) is characterized by sleep fragmentation [37] and has been associated with both short and long self-reported sleep time [22]. Given the association of OSA with cardiovascular disease [38], DM [39], and hypertension [40], OSA could potentially be confounding the reported association of sleep time and cardiovascular disease. Nevertheless, in the SHHS the association of sleep time with both hypertension and DM persisted after adjustment for OSA severity [22,32].

Potential mechanisms underlying the associations between sleep duration and poor health outcomes

Possible confounding by unmeasured health and lifestyle factors

A puzzling feature of the associations of sleep duration with mortality, cardiovascular disease, and metabolic measures is the lack of monotonicity: in the large majority of studies in adults, both short and long sleep durations are similarly associated with adverse outcomes. This problematic finding is often ignored by advocates of the view that short sleep duration is a cause of poor health. The explanation commonly offered for this observation is that long sleep duration may be a correlate of comorbid illness for which appropriate adjustment has not been made. The potential correlates of long sleep duration that may confound its association with poor health outcomes have been explored in greatest detail by Patel and colleagues [41]. Given the

sleep-inducing effects of a number of inflammatory cytokines [42,43], it is possible that subclinical inflammatory states, such as atherosclerosis, may lead to long sleep duration, although this is entirely speculative. (Conversely, there is growing literature on the possible proinflammatory effects of sleep deprivation, not reviewed here.) The potential for unmeasured comorbid illness applies equally, of course, to short sleep duration. In particular, insomnia is strongly associated with short sleep duration, and is also associated with increased autonomic nervous system and hypothalamic–pituitary–adrenal axis activity [44]. It is also possible that short sleep duration is a marker of an unhealthy lifestyle, which might include high levels of stress, poor diet, and sedentary lifestyle. Where insomnia and activity level have been included as covariates in the above studies, however, they have not explained the associations of sleep duration with mortality, coronary heart disease, DM, or hypertension. It is also noteworthy that in children, who are much less likely than adults to suffer from comorbid chronic illness, the relationship between sleep duration and obesity is monotonic rather than U-shaped. Although hardly a compelling finding, this is consistent with the view that short sleep duration has adverse health consequences, while long sleep duration is a marker of underlying chronic illness. Moreover, a recent study of the relationship between change in sleep duration and mortality found that among those sleeping for 6–8 h per night at baseline, a decrease in reported sleep duration over a 5-year interval was associated with a doubling of the adjusted risk of cardiovascular mortality [45]. Conversely, an increase in sleep duration from a baseline duration of 7 or 8 h per night was associated with a doubling of the risk for non-cardiovascular mortality, while an increase in sleep duration from a baseline duration of 5 or 6 h per night was associated with a non-significant decrease in cardiovascular mortality [45]. In the absence of experimental studies, however, it is not possible to conclude with confidence that short sleep duration at levels commonly occurring in the population are a cause of poor health outcomes.

Effect of experimental sleep restriction on blood pressure

While confounding of the associations by unmeasured environmental and lifestyle factors cannot be excluded in observational studies, experimental sleep deprivation studies provide compelling evidence that short sleep has an adverse impact on metabolic factors that are important causes of cardiovascular disease. A series of experiments conducted by Van Cauter and colleagues have convincingly demonstrated that sleep restriction to 4 h per night over a period of 1–5 days in healthy young adults causes insulin resistance, impaired glucose tolerance, delayed quiescence of cortisol excretion, and adverse effects on appetite and adipokine levels [7]. These findings have been recently reviewed by the same group [7] and will not be re-examined here.

Less extensive literature supports an association between sleep restriction and hypertension, which to our knowledge has not been similarly reviewed. Kato and colleagues found that morning SBP increased by a mean of 4 mmHg and DBP by a mean of 3 mmHg in a group of healthy adults (six men, two women; mean age 40 years) following a single night of total sleep deprivation [46]. Meier-Ewert and colleagues found a progressive increase in SBP across 3 days of total sleep deprivation, from a mean of 121.1 to 128.9 mmHg, in a sample of eight healthy men aged 22–37 years, with a smaller increase observed for DBP [47].

Several studies have demonstrated an increase in blood pressure after as little as 1 night of partial sleep deprivation. Tochikubo and colleagues found that, compared with a night of 8 h of sleep, mean SBP increased by 6 mmHg and mean DBP by 3 mmHg following 1 night of sleep restriction (to a mean duration of 3.6 h) as a result of working overtime, in a group of 18 male technical workers aged 23–48 years [48]. While this effect may be attributed to work stress, Lusardi and colleagues observed an increase of 4 mmHg in mean morning SBP but not DBP in healthy normotensive individuals (eight men, 10 women; age 24–30 years) after 1 night of experimental sleep restriction to 4 h at home [49]. The same group reported increases of 7 and 4 mmHg in mean morning SBP and DBP, respectively, in individuals with untreated mild to moderate hypertension (20 men, 19 women; age 34–68 years) after 1 night of sleep restriction to 4 h [50]. Irwin and Ziegler reported an even larger increase in blood pressure after a single night of sleep restriction to 4 h, which did not recover after 1 night of 8 h in bed, although this study did not compare these subjects with a group without sleep deprivation [51].

Two studies examined the effect of several nights of partial sleep deprivation. In a group of four men and six women aged 22–46 years, Muenter and colleagues reported very little difference in either SBP or DBP after sleep restriction to 4 h per night for 4 nights [52]. This study was designed to test the effect of sleep deprivation on orthostatic tolerance and, unlike the above studies, allowed continuation of usual caffeine intake and light exercise, and measured blood pressure in either the morning or the afternoon. In contrast, Meier-Ewert and colleagues reported striking increases of 22 mmHg in mean SBP and 17 mmHg in mean DBP after 10 days of sleep restriction to 4 h per night [47]. The sample size of four subjects was small, and the five control subjects also showed increases in mean SBP and DBP of 9.5 and 12.5 mmHg, respectively, suggesting

that other aspects of the protocol may have contributed to the increase.

As normal sleep is associated with decreased sympathetic nervous system activity [53], it has been postulated that increased activation of the sympathetic nervous system owing to prolonged wakefulness mediates the increased blood pressure observed in response to sleep deprivation. It has been reported that urinary epinephrine is increased during a night of partial sleep deprivation at home [50] or when sleep-deprived due to working overtime [48], and in the latter study, higher epinephrine excretion was also observed during the day, although the effects of sleep deprivation cannot be separated from those of work stress. Both time and frequency domain analyses of heart rate variability have suggested that partial sleep deprivation increases autonomic activity [48,54]. However, the importance of this mechanism has been challenged by two studies that found no increase in plasma catecholamine levels and a decrease in directly measured muscle sympathetic nerve activity following sleep deprivation, despite an increase in blood pressure [46,55]. In one study, imputed arterial baroreflex function was lower after total sleep deprivation [55], although a investigation that measured arterial baroreflex function from the heart rate response to nitroprusside and phenylephrine injection found no change following restriction of sleep to 4 h per night for 4 nights [52].

Alternative mechanisms include increased activity of the hypothalamic–pituitary–adrenal axis as a result of sleep deprivation. Cortisol secretion exhibits profound circadian variation, and sleep deprivation has been variously reported to cause a shorter quiescent period of plasma cortisol secretion and increased plasma cortisol levels during the afternoon and evening following either partial or total sleep deprivation [54,56], or a slight increase in plasma cortisol levels while maintaining a normal circadian profile [57]. Activation of the renin–angiotensin system by sleep deprivation has also been postulated, although 24 h of sleep deprivation was shown to blunt the nocturnal increase in plasma aldosterone and plasma renin activity [57]. The same group demonstrated variable plasma endothelin levels during sleep that paralleled changes in blood pressure and opposed the changes in plasma renin activity [58]. The possible role of endothelin in the hypertensive effect of sleep deprivation is unknown.

Possible confounding by genetic factors

While these experimental studies indicate that short-term severe sleep deprivation is likely to impair glucose tolerance and increase blood pressure, fewer than 1% of individuals report a habitual sleep duration of ≤4 h. The relevance of these studies to the levels of sleep deprivation that are common in the community remains uncertain. Before concluding that sleep durations of 5–6 h per night can cause adverse cardiovascular outcomes, we should consider an additional source of potential confounding that has received little attention. Many metabolic processes are under strong circadian influence, including glucose metabolism, hormone secretion, and feeding behavior (recently reviewed in [59]). Numerous studies have found that sleep duration and circadian preference are heritable traits; a finding recently replicated in the Framingham Heart Study Offspring cohort [60]. Several polymorphisms have been identified in core circadian clock genes that cause major derangements in circadian phenotype in both humans and lower vertebrate and invertebrate species; however, it is likely that many genes that are not part of the core clock mechanism are involved in the generation of sleep patterns and communication of the circadian rhythm from the suprachiasmatic nucleus to the periphery. Given the strong circadian pattern of metabolic processes, there is likely to be overlap between genes regulating sleep behaviors and those regulating metabolism. For example, heterozygous *Clock* mutant mice have a long free-running period of 27–28 h and have an increased energy intake, a change in the diurnal pattern of feeding, obesity, and hyperglycemia [61]. Both the Rev-erb nuclear receptors and the peroxisome proliferators-activated receptors [62] may provide links between circadian rhythms and metabolism. While we did not observe significant associations of sleep and circadian phenotypes with these gene families in a relatively small genome-wide association study [60], as ongoing investigations shed light on the genetic mechanisms underlying sleep regulation it will be important to look for co-regulated metabolic processes that may explain, in part, the association of sleep duration and adverse health outcomes.

Conclusion

A large body of evidence demonstrates that short sleep duration is associated with hypertension, DM, coronary heart disease, and mortality. Although the mechanisms underlying these associations remain to be elucidated, a preponderance of evidence suggests a causal association, especially at very short sleep durations. While there is undoubtedly individual variation in sleep need, and no study has demonstrated that sleep extension to 7–8 h per night reduces cardiovascular risk, data from studies of neurocognitive function suggest that very few individuals obtain sufficient amounts of sleep when sleeping for as little as 6 h per night. The common clinical recommendation to obtain 7–8 h of sleep per night is therefore prudent, and should be considered an important component of a healthy lifestyle. Voluntary chronic partial sleep deprivation has become a social norm, however, and increased sleep duration must come at the expense of other pursuits.

Table 5. Practical guidelines to increase sleep duration.

Identify specific barriers to increasing sleep time and suggest specific measures to overcome these barriers
Develop a consistent sleep schedule with a regular bedtime and rise time
Avoid delaying sleep time on the weekends by more than 1–2 h
Relax and decrease activity 60 min before scheduled bedtime
Avoid caffeinated beverages late in the day
Avoid heavy meals near bedtime
Exercise in the afternoon and early evening but not within 2 h of bedtime
Avoid drinking large amounts of fluid late in the evening to prevent awakening owing to full bladder
Avoid watching television or working on the computer in the bedroom

Perhaps the most important contribution a healthcare provider can make is to educate patients about the potential risks of a short sleep duration in order to motivate a change in sleep behavior. One should also attempt to identify the specific activities that prevent the patient from obtaining adequate sleep and provide concrete suggestions to overcome these impediments, such as recording a late-night television show for viewing earlier the following evening or setting a specific cut-off time for computer use, along with good general sleep hygiene (Table 5).

Disclosures

The authors have no relevant financial interests to disclose.

References

1. Hammond EC. Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women. *Am J Public Health Nations Health* 1964;**54**:11–23.
2. National Sleep Foundation. *Sleep in America Poll*. Washington, DC, USA: National Sleep Foundation, 2003.
3. National Sleep Foundation. *Sleep in America 2000*. Washington, DC, USA: National Sleep Foundation, 2000.
4. Wehr TA, Moul DE, Barbato G et al. Conservation of photoperiod-responsive mechanisms in humans. *Am J Physiol* 1993;**265**:R846–57.
5. Klerman EB, Dijk DJ. Interindividual variation in sleep duration and its association with sleep debt in young adults. *Sleep* 2005;**28**:1253–9.
6. Van Dongen HP, Maislin G, Mullington JM et al. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;**26**:117–26.
7. Knutson KL, Spiegel K, Penev P et al. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;**11**:163–78.
8. Taheri S. The interactions between sleep, metabolism, and obesity. *Int J Sleep Wakefulness* 2007;**1**:14–23.
9. Pollak CP, Perlick D, Linsner JP et al. Sleep problems in the community elderly as predictors of death and nursing home placement. *J Community Health* 1990;**15**:123–35.
10. Kripke DF, Simons RN, Garfinkel L et al. Short and long sleep and sleeping pills. Is increased mortality associated? *Arch Gen Psychiatry* 1979;**36**:103–16.
11. Kripke DF, Garfinkel L, Wingard DL et al. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002;**59**:131–6.
12. Wingard DL, Berkman LF. Mortality risk associated with sleeping patterns among adults. *Sleep* 1983;**6**:102–7.
13. Patel SR, Ayas NT, Malhotra MR et al. A prospective study of sleep duration and mortality risk in women. *Sleep* 2004;**27**:440–4.
14. Tamakoshi A, Ohno Y; JACC Study Group. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. *Sleep* 2004;**27**:51–4.
15. Kojima M, Wakai K, Kawamura T et al. Sleep patterns and total mortality: a 12-year follow-up study in Japan. *J Epidemiol* 2000;**10**:87–93.
16. Amagai Y, Ishikawa S, Gotoh T et al. Sleep duration and mortality in Japan: the Jichi Medical School Cohort Study. *J Epidemiol* 2004;**14**:124–8.
17. Appels A, de Vos Y, van Diest R et al. Are sleep complaints predictive of future myocardial infarction? *Act Nerv Super (Praha)* 1987;**29**:147–51.
18. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *Am J Epidemiol* 1992;**135**:854–64.
19. Schwartz SW, Cornoni-Huntley J, Cole SR et al. Are sleep complaints an independent risk factor for myocardial infarction? *Ann Epidemiol* 1998;**8**:384–92.
20. Newman AB, Spiekerman CF, Enright P et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *J Am Geriatr Soc* 2000;**48**:115–23.
21. Carskadon MA, Dement WC, Mitler MM et al. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiatry* 1976;**133**:1382–8.
22. Gottlieb DJ, Redline S, Nieto FJ et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006;**29**:1009–14.
23. Partinen M, Putkonen PT, Kaprio J et al. Sleep disorders in relation to coronary heart disease. *Acta Med Scand Suppl* 1982;**660**:69–83.
24. Ayas NT, White DP, Manson JE et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med* 2003;**163**:205–9.
25. Meisinger C, Heier M, Löwel H et al. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA augsburg cohort study. *Sleep* 2007;**30**:1121–7.
26. Qureshi AI, Giles WH, Croft JB et al. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. *Neurology* 1997;**48**:904–11.
27. Ayas NT, White DP, Al-Delaimy WK et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003;**26**:380–4.
28. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care* 2005;**28**:2762–7.
29. Bjorkelund C, Bondyr-Carlsson D, Lapidus L et al. Sleep disturbances in midlife unrelated to 32-year diabetes incidence: the prospective population study of women in Gothenburg. *Diabetes Care* 2005;**28**:2739–44.
30. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;**29**:657–61.
31. Gangwisch JE, Heymsfield SB, Boden-Albala B et al. Sleep duration as a risk factor for diabetes incidence in a large US sample. *Sleep* 2007;**30**:1667–73.
32. Gottlieb DJ, Punjabi NM, Newman AB et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005;**165**:863–7.
33. Cappuccio FP, Stranges S, Kandala NB et al. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. *Hypertension* 2007;**50**:693–700.
34. van den Berg JF, Tulen JH, Neven AK et al. Sleep duration and hypertension are not associated in the elderly. *Hypertension* 2007;**50**:585–9.
35. Bjorvatn B, Sagen IM, Øyane N et al. The association between sleep duration, body mass index and metabolic measures in the Hordaland Health Study. *J Sleep Res* 2007;**16**:66–76.
36. Gangwisch JE, Heymsfield SB, Boden-Albala B et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;**47**:833–9.
37. Gottlieb DJ, Whitney CW, Bonekat WH et al. Relation of sleepiness to respiratory disturbance index. The Sleep Heart Health Study. *Am J Respir Med* 1999;**159**:502–7.
38. Shahar E, Whitney CW, Redline S et al. Sleep disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;**163**:19–25.
39. Punjabi NM, Sorkin JD, Katzel LI et al. Sleep disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002;**165**:677–82.
40. Peppard PE, Young T, Palta M et al. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378–84.
41. Patel SR, Malhotra A, Gottlieb DJ et al. Correlates of long sleep duration. *Sleep* 2006;**29**:881–9.
42. Obal F Jr, Opp M, Cady AB et al. Interleukin 1 alpha and an interleukin 1 beta fragment are somnogenic. *Am J Physiol* 1990;**259**:R439–46.
43. Kapas L, Hong L, Cady AB et al. Somnogenic, pyrogenic, and anorectic activities of tumor necrosis factor-alpha and TNF-alpha fragments. *Am J Physiol* 1992;**263**:R708–15.
44. Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. *Sleep Med Rev* 2007;**11**:71–9.
45. Ferrie JE, Shipley MJ, Cappuccio FP et al. A prospective study of change in sleep duration: Associations with mortality in the Whitehall II cohort. *Sleep* 2007;**30**:1659–66.

46. Kato M, Phillips BG, Sigurdsson G et al. Effects of sleep deprivation on neural circulatory control. *Hypertension* 2000;**35**:1173–5.
47. Meier-Ewert HK, Ridker PM, Rifai N et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 2004;**43**:678–83.
48. Tochikubo O, Ikeda A, Miyajima E et al. Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. *Hypertension* 1996;**27**:1318–24.
49. Lusardi P, Mugellini A, Preti P et al. Effects of a restricted sleep regimen on ambulatory blood pressure monitoring in normotensive subjects. *Am J Hypertens* 1996;**9**:503–5.
50. Lusardi P, Zoppi A, Preti P et al. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. *Am J Hypertens* 1999;**12**:63–8.
51. Irwin MR, Ziegler M. Sleep deprivation potentiates activation of cardiovascular and catecholamine responses in abstinent alcoholics. *Hypertension* 2005;**45**:252–7.
52. Muenter NK, Watenpaugh DE, Wasmund WL et al. Effects of sleep restriction on orthostatic cardiovascular control in humans. *J Appl Physiol* 2000;**88**:966–72.
53. Somers VK, Dyken ME, Mark AL et al. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* 1993;**328**:303–7.
54. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;**354**:1435–9.
55. Ogawa Y, Kanbayashi T, Saito Y et al. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep* 2003;**26**:986–9.
56. Leproult R, Copinschi G, Buxton O et al. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 1997;**20**:865–70.
57. Charloux A, Gronfier C, Chapotot F et al. Sleep deprivation blunts the night time increase in aldosterone release in humans. *J Sleep Res* 2001;**10**:27–33.
58. Charloux A, Piquard F, Geny B et al. Circulating endothelin parallels arterial blood pressure during sleep in healthy subjects. *Regul Pept* 2004;**119**:133–8.
59. Ramsey KM, Marcheva B, Kohsaka A. The clockwork of metabolism. *Annu Rev Nutr* 2007;**27**:219–40.
60. Gottlieb DJ, O'Connor GT, Wilk JB. Genome-wide association of sleep and circadian phenotypes. *BMC Med Genet* 2007;**8**:S9.
60. Turek FW, Joshu C, Kohsaka A et al. Obesity and metabolic syndrome in circadian *Clock* mutant mice. *Science* 2005;**308**:1043–5.
62. Staels B. When the *Clock* stops ticking, metabolic syndrome explodes. *Nat Med* 2006;**12**:54–5.

CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

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

SLEEP-DISORDERED BREATHING

Obesity and risk of sleep related upper airway obstruction in Caucasian children

Kohler M, Lushington K, Couper R et al.
J Clin Sleep Med 2008;**4**:129–36.

The authors of this study examined the interaction between obesity, age, and upper airway obstruction in an Australian population of Caucasian children. Obesity, but not age, was found to be a significant but weak predictor of upper airway obstruction during sleep.

Childhood obesity is a significant health problem and its incidence has risen over the past decade. It is thought that childhood obesity is a risk factor for upper airway obstruction during sleep; however, the effects of age and ethnicity on this relationship are not well known. The majority of studies have included participants of mixed ethnic groups, and those that have comprised largely single ethnic groups have suggested discrepancies between them. Furthermore, an older age may confer a stronger association between obesity and obstructive sleep apnea syndrome (OSAS) in children, although few trials have investigated this matter.

In this study, the authors investigated the interaction between obesity, age, and upper airway obstruction in 190 Caucasian children, aged 4–12 years, living in Australia. Participants had been referred for evaluation of upper airway obstruction at a sleep disorders unit between October 1999 and December 2003. They were classified by polysomnography and parental responses to the question "Does your child snore?" as infrequent snorers (n=80), habitual snorers (n=68), or as having OSAS (n=42). Body mass index (BMI) z-scores were calculated for each child using growth charts.

In total, 66 out of the 190 children were overweight or obese. Children with OSAS were the most likely to be overweight or obese (52% compared with 30% for infrequent snorers and 29% for habitual snorers). Significant positive correlations between BMI z-score and the number of obstructive and central respiratory events during sleep, as well as the frequency of respiratory arousals, were found. A higher BMI z-score also correlated with lower SpO_2 nadir. In addition, older age was associated with fewer central apneas. OSAS was seen more often in younger children (aged <8 years), but there was no significant difference in sleep disordered breathing subtypes between children aged <8 years and those aged ≥8 years.

In conclusion, these results suggest that obesity is a significant but weak predictor of OSAS in this patient population. They also indicate that age may not be a significant predictor of upper airway obstruction.

Address for reprints: M Kohler, Centre for Sleep Research, The University of South Australia, Level 7, Playford Building, City East Campus, Frome Road, SA, Australia 5000. Email: mark.kohler@unisa.edu.au

Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy

Chihorek AM, Abou-Khalil B, Malow BA.
Neurology 2007;**69**:1823–7.

In a novel approach to further examine the etiology of late-onset seizures in older adults with epilepsy, the present authors conducted a cross-sectional study of epilepsy patients to determine whether obstructive sleep apnea is a contributing factor to seizures in this patient group.

This study included 21 patients with late-onset seizures with epilepsy in the absence of stroke, tumor, or degenerative disease. Patients were divided into two groups by a blinded epilepsy specialist. Group one (n=11; 82% male) included patients with seizure onset at ≥50 years of age or seizure onset before then with an increase in seizure frequency at the age of 50 years. Group two (n=10; 20% male) included patients with seizure onset before 50 years of age but with either stable or improved seizure frequency after the age of 50 years.

The groups did not differ in age, body mass index, neck circumference, number of epileptic drugs, or frequency of nocturnal seizures. Of the patients, 29% had an apnea–hypopnea index (AHI) of ≥15 events/h. The AHI was greater in group one, with a mean of 23.2 events/h of sleep, compared with an AHI of 3.1 events/h in group two.

Interestingly, the moderate AHI found in group one patients suggests that obstructive sleep apnea (OSA) may be a contributing factor in late-onset seizures with epilepsy. The investigators were able to examine long-term treatment of OSA with continuous positive airway pressure (CPAP) use in only a few of the subjects, with results indicating a reduction in nocturnal seizure frequency. A long-term follow-up study of the use of CPAP in the treatment of OSA in this study population could provide beneficial information in late-onset epiliepsy patients. Furthermore, the results may be related to sleep loss, although follow-up studies are needed to investigate this.

Address for reprints: BA Malow, Vanderbilt University Department of Neurology, Medical Center North, Room A-0118, 1161 21st Avenue South, Nashville, TN 37232–2551, USA.
Email: beth.malow@vanderbilt.edu

Pediatric obstructive sleep apnea and quality of life: a meta-analysis

Baldassari CM, Mitchell RB, Schubert C et al.
Otolaryngol Head Neck Surg 2008;**138**:265–73.

This meta-analysis examined the effect of obstructive sleep apnea (OSA) on quality of life (QoL) in children. The authors found that pediatric OSA has a significant impact on QoL, similar to that of juvenile rheumatoid arthritis, but long-term improvements in QoL can be achieved in pediatric OSA patients following adenotonsillectomy.

The authors of this article emphasize the importance of considering quality of life (QoL) outcomes following adenotonsillectomy, and conducted a meta-analysis of QoL in pediatric obstructive sleep apnea (OSA) patients before and after surgery.

A literature search of PubMed yielded 10 articles published during 1970–2005 that met the following inclusion criteria:

- Cases of sleep-disordered breathing diagnosed by clinicians or polysomnography.
- Patients aged 1–18 years.
- Data on health-related QoL gathered using the Child Health Questionnaire (CHQ), or evaluation of outcomes following adenotonsillectomy using the OSA-18 QoL survey.
- Short- or long-term QoL data collected ≥4 weeks and ≥6 months after adenotonsillectomy, respectively.

The 10 studies included a total of 562 children with OSA, 93 children with juvenile rheumatoid arthritis (JRA), and 815 healthy children. In eight of the 12 CHQ subscale QoL items, scores of children with OSA were significantly lower than those of healthy children, particularly with respect to the CHQ QoL subscales of general health perceptions and parental impact-emotional ($p<0.001$ for both). Two studies compared CHQ QoL scores for OSA and JRA, and found that – with the exception of subscales of parental impact-emotional and parental impact-time, which both significantly yielded lower scores for children with OSA ($p<0.05$ for both) – children with OSA had a similarly low QoL as those with JRA.

Short- and long-term outcomes following adenotonsillectomy were reported in seven and two studies, respectively. Overall, significant improvements in both short- and long-term QoL were observed following surgery, with the most significant changes made in sleep disturbance, caregiver concerns, and physical suffering. Furthermore, there were no significant differences between short-term and long-term scores.

The authors' remark on the similarity of QoL scores observed in children with OSA and JRA, and emphasize that further research is needed to explain why the apparently benign condition of OSA causes as much suffering as the presently uncurable, chronic condition. As OSA can severely affect a child's QoL, including their daytime functioning, behavior, and family interactions, the apparent long-term benefits of adenotonsillectomy indicated in this meta-analysis warrants further research on the use of surgery to treat pediatric OSA.

Address for reprints: CM Baldassari, Department of Otolaryngology-Head and Neck Surgery, Virginia Commonwealth University Medical Center, Richmond, VA 23298, USA. Email: cbaldassari@mcvh-vcu.edu

Pulse transit time as a screening test for pediatric sleep-related breathing disorders.

Brietzke SE, Katz ES, Roberson DW.
Arch Otolaryngol Head Neck Surg 2007;**133**:980–4.

As overnight polysomnography (PSG) for detection of sleep-disordered breathing in children is limited by inconvenience and cost, the authors of this study proposed using pulse transit time (PTT) as a screening tool for these disorders. The authors of this study compared the results of PSG and simultaneous PTT from a sample of 59 patients with a mean age of 7.8 years. The PTT arousal index demonstrated a diagnostic utility akin to PSG in patients with moderate and severe cases of obstructive sleep apnea/hypopnea syndrome.

Overnight polysomnography (PSG) remains the "gold standard" for the diagnosis of sleep-disordered breathing in

children, but it is inconvenient, expensive, and not always available. Pulse oximetry and other screening tools have also been used for diagnostic purposes; however, none has been proven to be accurate. The authors of this study suggest that pulse transit time (PTT) may be an accurate screening tool to rule out the diagnosis of obstructive sleep apnea/hypopnea syndrome (OSAHS) in children.

The PTT arousal index is a non-invasive measure of arousal that reveals alterations in blood pressure patterns associated with respiratory arousals from sleep. Two objectives were undertaken in this study – firstly, the assessment of congruity between the PTT index and overnight PSG in detecting OSAHS in the pediatric population and, secondly, comparison of the results of PTT with that of continuous pulse oximetry during the over-night PSG.

In total, 59 patients aged 2–16 years (mean 7.8 years), who presented for a routine PSG were enrolled in the study. Patients who were obese, had craniofacial syndromes (n=15), and those with (n=11) a history of adenotonsillectomy were included in the cohort. The mean apnea–hypopnea index (AHI) was 4.5 events/h. When comparing the two data sets, the PTT index showed a high correlation with the PSG-determined AHI ($p<0.001$). This relationship remained significant in patients with craniofacial syndromes in addition to those with and without adenotonsillar tissue. A similar comparison between PTT and pulse oximetry measurements failed to show a significant correlation.

Interestingly, it is not clear why there was no significant association between PTT and pulse oximetry, as the former incorporates the measurements of the latter as part of its algorithm and is linked to the AHI. Furthermore, there is no mention of the utility of an ambulatory PSG, which is also employed as a screening tool to eliminate the diagnosis of OSAHS among the pediatric population, as it is less costly and more convenient than an overnight PSG.

Address for reprints: SE Brietzke, Department of Otolaryngology, Walter Reed Army Medical Center, 6900 Georgia Avenue, Washington, DC 20307, USA. Email: sebrietzke@msn.com

Elevated levels of neopterin in sleep-disordered breathing

Punjabi NM, Beamer BA, Jain A.
Chest 2007;**132**:1124–30.

The current authors examined neopterin levels in patients with and without sleep-disordered breathing (SDB) together with nocturnal oxyhemoglobin desaturation and sleep-stage distribution. Their results suggest that the severity of SDB is independently associated with serum levels of neopterin.

The relationship between hypertension and sleep-disordered breathing (SDB) is widely known; however, the pathophysiology is still under investigation. In previous studies, high levels of neopterin have been correlated with adverse coronary events and acute myocardial infarction. The current authors further investigated neopterin levels in relation to SDB severity.

Fasting blood samples were taken from 55 men referred for overnight polysomnography (PSG; mean age 41 years, mean body mass index [BMI] 30.3). An average degree of oxyhemoglobin desaturation was used as an index of nocturnal hypoxemia stress. Subjects were divided into four groups based on apnea–hypopnea index (AHI) events per hour severity. Average adjusted neopterin levels were also measured. The results indicate a linear trend in neopterin levels from mild to severe AHI: no SDB, AHI <3.8 (neopterin 6.9 ng/mL); mild SDB, AHI 3.8–11.9 (7.1 ng/m); moderate SDB, AHI 11.9–36.8 (7.7 ng/mL); severe SDB, AHI >36.8 (9.0 ng/mL). In sleep-stage distribution neopterin level analysis revealed independent correlations between stages one and two. These correlations were absent in slow-wave and rapid eye movement sleep.

This study showed that neopterin levels were higher in subjects with moderate-to-severe SDB along with a greater degree of nocturnal hypoxemia when controlling for BMI, waist circumference, and percentage of body fat. The increased levels of neopterin further emphasize the association between SDB and macrophage activation.

Address for reprints: NM Punjabi, Johns Hopkins University, Division of Pulmonary and Critical Care Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA. Email: npunjabi@jhmi.edu

Apnea promotes glutamate-induced excitotoxicity in hippocampal neurons

Fung SJ, Xi MC, Zhang JH et al.
Brain Res 2007;**1179**:42–50.

The current investigators explored obstructive sleep apnea and hippocampal-dependant cognitive deficits. Single stimulus-evoked field excitatory post-synaptic potentials were examined in order to investigate monosynaptic transmission of cornu ammonis region 3 (CA3)–CA1 synapses *in vivo*.

Previous studies have shown that rats with chronic hypoxia have marked apoptosis in the cornu ammonis 1 (CA1) region of the hippocampus, while other investigations have found that humans with obstructive sleep apnea (OSA) have significant loss of gray matter in this region.

In the present study results were obtained from guinea pigs in control (pre-apneic), apneic, and post-apneic conditions. In the post-apneic group high increases in field

excitatory post-synaptic potential (fEPSP) amplitude and slope occurred. For most animals, recovery occurred within 15 min. Change in paired-pulse plasticity of CA3–CA1 synapses indicated that apnea attenuated paired-pulse facilitation in slope and amplitude. Recurrent apnea episodes were used to evaluate potential morphological signs of neuronal damage. Study animals showed labeled neurons in CA1 whereas controls had none. This suggests excitotoxic effects of repeated release of glutamate in hippocampal areas.

The implications of the current study help detail the temporal course of reversible changes in CA1 and shed light onto the neurological deficits that can result from obstructive sleep apnea.

Address for reprints: SJ Fung, WebSciences International, 1251 Westwood Boulevard, Los Angeles, CA 90024, USA. Email: sfung@websciences.org

Comparison of sleep parameters at titration and subsequent compliance between CPAP-pretreated and non-CPAP-pretreated patients with obstructive sleep apnea

Suzuki M, Saigusa H, Furukawa T.
Sleep Med 2007;**8**:773–8.

The objective of this study was to assess the effect of continuous positive airway pressure (CPAP) pretreatment on various sleep parameters of patients with obstructive sleep apnea (OSA) in a formal inpatient titration study. A prospective randomized study was undertaken that included an equal number of patients with OSA who were either pretreated with CPAP for 2 months or untreated. All patients then underwent a formal polysomnographic (PSG) titration. Although pretreatment with CPAP did not significantly affect any sleep parameters during the formal titration study, it did increase the sleep efficiency of patients who showed lower sleep efficiency on the initial PSG which, indirectly, may increase compliance to future CPAP treatment.

It may be difficult to ascertain the efficacy of continuous positive airway pressure (CPAP) for an individual if they have previously encountered difficulties during a formal titration study. It is likely that they will not want to use an apparatus they found burdensome and uncomfortable during their first encounter. The authors of the present study aimed to determine whether a previously protracted encounter with CPAP affected various sleep parameters and, more importantly, the rate of compliance among patients who have undergone CPAP prior to a formal inpatient titration study.

A randomized controlled study was undertaken with 140 patients whose initial polysomnographic (PSG) findings revealed an apnea–hypopnea index (AHI) ≥20 events/h. These patients were divided into two sets of 70 individuals; one group received an auto-adjusted CPAP unit to use for 2 months prior to a formal titration study, while the other did not. There were no significant differences between the groups with regard to age, body mass index, and baseline PSG parameters; however, the majority of the subjects were male, with only 5 female subjects in the whole cohort.

During the formal titration study the sleep efficiency of the CPAP pretreated group was significantly higher than that of the non-treated group (p=0.002). Furthermore, there was a significant difference in changes in the arousal index during non-rapid eye movement sleep between the two groups (p=0.036). No other significant differences in sleep parameters were observed. Nine months after the titration study, the average daily use of CPAP was similar between the groups; however, there was a significant difference between pre- and post-titration CPAP compliance in the pre-treated group. Moreover, at this timepoint, eight patients in the non-pretreated group discontinued treatment, whereas only one patient discontinued use in the pre-treated group.

Although the authors conclude that compliance with CPAP may be higher in pretreated patients whose sleep efficiency was low during the initial PSG recording, they do not provide specific results and analyses to fully support this statement. Furthermore, it would be difficult to compare various sleep parameters on two very different studies as sleep architectural changes themselves are influenced by CPAP. Nevertheless, this study does broach practical issues that are relevant to clinicians treating non-compliant patients with OSA who utilize CPAP.

Address for reprints: M Suzuki, Department of Otolaryngology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, 173-8605 Tokyo, Japan. Email: suzukima@med.teikyo-u.ac.jp

Evaluation of autoCPAP devices in home treatment of sleep apnea/hypopnea syndrome

Meurice JC, Cornette A, Philip-Joet F et al.; ANTADIR "PPC" working group.
Sleep Med 2007;**8**:695–703.

This study compared fixed and auto-adjust continuous positive airway pressure (CPAP) devices in terms of polysomnography criteria, daytime vigilance, and quality of life. The results indicate that auto-adjust CPAP is as efficacious as fixed CPAP for the treatment of sleep apnea/hypopnea syndrome.

With rising healthcare costs the need for home treatment of sleep apnea/hypopnea syndrome (SAHS) has been growing. Several auto-adjust continuous positive airway pressure

(autoCPAP) devices are currently on the market, although studies on tolerance and long-term effectiveness are few.

The current investigators tested five CPAP devices in a prospective randomized, multicenter trial. Group one used a fixed CPAP device that had positive pressure manually determined in a laboratory titration. The other four groups were treated with different autoCPAP machines for 6 months. Data were gathered on compliance, quality of life as measured by the Short Form-36 (SF-36) questionnaire, and daytime vigilance as measured by the Epworth Sleepiness Scale (ESS), at baseline and 6-month follow-up.

The study comprised 83 patients (mean age 56 years, body mass index 30.8) with a severe apnea–hypopnea index (AHI; 52.3 events/h). All groups had an increase in slow-wave and rapid eye movement sleep, with a significant reduction in stage 1–2 sleep, the time spent <90% blood oxygen saturation, and in AHI score compared with baseline. All groups showed significant improvement in ESS scores, but SF-36 scores did not improve. Compliance was >5 h/night, with no significant differences between the groups.

The current study helps demonstrate that autoCPAP devices reduce AHI and improve daytime sleepiness as effectively as fixed CPAP, with good compliance rates, in patients with SAHS.

Address for reprints: JC Meurice, Service de Pneumologie, 2 Rue de la Milétrie, CHU de Poitiers, 86000 Poitiers, France.
Email: meurice@chu-poitiers.fr

Cost-effectiveness and degree of satisfaction with home sleep monitoring in patients with symptoms of sleep apnea

Jurado Gámez B, Redel Montero J, Muñoz Cabrera L et al. *Arch Bronconeumol* 2007;**43**:605–10.

Home sleep monitoring is gaining increased attention as a potential means of diagnosing sleep apnea/hypopnea syndrome (SAHS). In the present study participants completed both polysomnography (PSG) in a sleep laboratory and home monitoring, and rated their satisfaction with each. The results suggest that home monitoring is a cost-effective and valid alternative to PSG, especially in those with more severe SAHS symptoms.

The authors of this study compared the cost of polysomnography (PSG) in a sleep laboratory with that of home sleep monitoring, as well as patient satisfaction with each procedure and the validity of home monitoring as a test for sleep/apnea hypopnea syndrome (SAHS).

The participants comprised patients consecutively referred to a sleep-disordered breathing unit of an academic medical center with a high pre-test probability of SAHS. In all, 52 patients (aged 52±9 years, 10 women) completed both PSG and home monitoring (6 h each) in a random order. PSG included all the traditional channels, while home monitoring included airflow (pressure sensor and thermistor), heart rate, tracheal microphone, chest/abdominal effort, blood oxygen saturation (SaO_2), body position, and leg electromyogram. After each sleep recording participants completed a 10-point visual analogue scale measuring their satisfaction with the procedure.

On average, home monitoring cost €140 (US$220) and PSG cost €250 (US$400). Satisfaction with home monitoring was significantly higher than satisfaction with PSG (median score 9/10 vs. 7/10; p<0.0001). High, significant correlations were observed between the results of both methods (i.e. r=0.97 for apnea–hypopnea index [AHI], r=0.89 for number of SaO_2 desaturations >3%, r=0.71 for time with SaO_2 <90%). According to receiver operating characteristics analyses, when an AHI ≥10 was used to diagnose SAHS by PSG, the cutoff AHI of 5.6 on home monitoring yielded a sensitivity of 89% and specificity of 80%. When AHI ≥30 on PSG was used to diagnose SAHS, an AHI of 26.4 on home monitoring had 100% sensitivity and specificity.

The authors concluded that home monitoring is a cost-effective alternative to sleep-laboratory PSG with which patients are likely to be highly satisfied. Home monitoring appears to be most valid in those with a high pre-test probability of severe SAHS.

Address for reprints: B Jurado Gámez, Servicio de Neumología, Hospital Universitario Reina Sofía, Córdoba, España.
Email: bjg01co@hotmail.com

Detection of flow limitation in obstructive sleep apnea with an artifical neural network

Norman RG, Rapoport DM, Ayappa I. *Physiol Meas* 2007;**28**:1089–100.

The authors of this study used an artificial neural network for the automated detection of flow limitations from air flow signals obtained during polysomnography; breath-by-breath agreement with traditional human scoring was up to 82%. Although the authors conclude that this automated neural network approach could be used to provide a standardized, reproducible, and automated means of detecting upper airway resistance, it should be noted that the feasibility of this approach rests on the authors' claim that a plateau in the inspiratory airflow–time contour reliably reflects airway collapsibility.

There is good reason to develop valid, reliable, automated scoring procedures for physiological parameters: this could potentially save time and allow standardization and

reproducibility of scoring beyond what is achievable with traditional human rating. In this study, Norman and colleagues attempt to utilize an artificial neural network to automatically detect flow limitations from air flow signals obtained during polysomnography. The target phenomena are variable and the signal likely affected by noise; therefore, it seems logical to use an artificial neural network (a computer algorithm modeled on the biological nervous system) for this task, as they are well-suited to detecting "fuzzy" phenomena of this sort.

The study procedure involved training the network on randomly selected breaths of a training set and then testing it versus human scoring (i.e. visual inspection of the air flow–time curve) on the remaining breaths of the dataset and a naïve dataset. The rates of agreement with manual scoring were 71% and 58%, respectively. However, combination of the "probably normal" and "normal" categories, and the "probably flow limited" and "flow limited" categories increased agreement to 89% and 82%, respectively.

The authors conclude that this automated neural network approach could be used to provide a standardized, reproducible, and automated means of detecting upper airway resistance. It is important to note, however, that the utility of this study rests on the authors' assertion that a plateau in the inspiratory airflow–time curve provides a non-invasive indicator of airway collapsibility.

Address for reprints: I Ayappa, Division of Pulmonary and Critical Care Medicine, NYU School of Medicine, New York, NY 10016, USA.
Email: indu.ayappa@medinyu.edu

Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy

Gozal D, Kheirandish-Gozal L, Serpero LD et al.
Circulation 2007;**116**:2307–14.

Endothelial dysfunction is a hallmark of vascular disease and a main mechanism in diminishing nitric oxide. It has been linked to obstructive sleep apnea (OSA) in adult populations. The current authors investigated endothelial function in non-obese children diagnosed with OSA. The results suggest that adenotonsillectomy may help improve endothelial function in these children.

In adult populations it has been shown that soluble CD40 ligand (sCD40L) concentrations can be used to monitor pro-atherosclerotic states that can result from obstructive sleep apnea (OSA). The authors of the current study utilized a surrogate marker for endothelial function, hyperemic response, in children with OSA before and after adenotonsillectomy.

Non-obese children aged 6–11 years with an apnea–hypopnea index (AHI) of >5 events/h (n=26) were compared with a control group of children with an AHI <1 event/h (n=8) based on standard polysomnography (PSG) procedures. Each child had a follow-up PSG at 4–6 months following treatment. Endothelial function was assessed with a modified hyperemic test and plasma level of sCD40L was measured in each child.

The results show that endothelial function measured by hyperemic response was significantly blunted in OSA children compared with the control group. At the follow-up visit, responses in the adenotonsillectomy group had significantly improved (normalized in 77%). Significant improvements in sCD40L levels were also seen at the follow-up visit. Weak linear correlations were found between sCD40L and AHI. A family history of ischemic heart disease was significantly correlated with endothelial dysfunction even after treatment of OSA.

The current study increases the understanding of endothelial function in children with OSA, as well as the contributing factors of treatment and family history. Most of the children showed a benefit at follow-up, suggesting that the adenotonsillectomy helped improve endothelial function. In addition, an improvement of sCD40L concentration with adenotonsillectomy occurred in the study group; however, this was not seen in children with a strong family history of ischemic heart disease.

Address for reprints: D Gozal, Kosair Children's Hospital Research Institute, University of Louisville School of Medicine,
570 South Preston Street, Suite 204, Louisville, KY 40202, USA.
Email: david.gozal@louisville.edu

SLEEP-RELATED MOVEMENT DISORDERS

Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study

Winkelman JW, Shahar E, Sharief I et al.
Neurology 2008;**70**:35–42.

In this large cross-sectional cohort study, the investigators demonstrated that restless legs syndrome (RLS) is independently associated with an increased risk of cardiovascular disease (CVD). The risk of CVD in subjects with RLS was approximately twice that of those without RLS; this association appeared to be strongest in those with more frequent or severe RLS symptoms.

An association between cardiovascular disease (CVD) and restless leg syndrome (RLS) has been indicated in two epidemiological studies [1,2]. However, the diagnostic criteria for

RLS have changed since these analyses were published, and one of the studies included data only from men. The mechanism underlying a relationship between CVD and RLS is unclear, but may involve repetitive electroencephalograhic arousals, substantial autonomic hyperactivity, or sleep deprivation.

The present authors conducted a cross-sectional observational study of 3433 individuals enrolled in the US Sleep Heart Health Study. Subjects had a mean age of 67.9 years, 80% were white, and 56% were women. Diagnoses of RLS were based on positive responses on a self-administered questionnaire, and diagnoses of CVD included patient self-reports of diagnoses made by doctors and physician-diagnosed stroke and heart failure.

The investigators determined that RLS was present in 5.2% of this cohort, and affected 6.8% of women and 3.3% of men. The demographic characteristics of subjects with and without RLS were similar, although those without RLS were more likely to consume >1 alcoholic drink per day. CVD was experienced by 29.6% and 19.5% of RLS and non-RLS subjects, respectively. The following variables were also associated with a significantly higher risk of CVD:

- Older age.
- Male sex.
- Diabetes.
- Ratio of total to high-density lipoprotein cholesterol.
- Self-reported sleep onset latency.
- Smoking.
- Use of hypertensive medications.

However, multivariate analysis demonstrated that RLS was independently associated with an increased risk for both CVD and coronary artery disease (CAD), with odds ratios of 2.07 (95% confidence interval [CI] 1.43–3.00) and 2.05 (95% CI 1.38–3.04), respectively. Subjects with symptoms of RLS >16 times per month and those with severely bothersome symptoms were more likely to be affected by CVD and CAD than those with less frequent and less severe symptoms.

Although these authors demonstrate that there is an independent association between RLS and CVD, further studies are required to determine whether these findings can be applied to younger populations and different ethnic groups. The underlying mechanisms of this relationship also require further elucidation.

1. Ulfberg J, Nyström B, Carter N et al. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord* 2001;**16**:1159–63.
2. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* 2006;**7**:545–52.

Address for reprints: J Winkelman, Division of Sleep Medicine, Brigham & Women's Hospital, Harvard Medical School, 1505 Commonwealth Avenue, Brighton, MA 02135, USA.
Email: jwinkelman@sleephealth.com

Patterns of treatment for restless legs syndrome in primary care in the United Kingdom

Martinez C, Finnern HW, Rietbrock S et al.
Clin Ther 2008;**30**:405–18.

These authors analyzed a large sample of patients with RLS from a primary care perspective. They examined the frequencies of prescriptions, referrals, laboratory tests and comorbidities in comparison with a control population.

Symptoms of restless legs syndrome (RLS) have been reported to occur in 5–11% of European populations. In the primary care setting, the prevalence of this disorder is approximately 1–3% and is more common in females than males. In 2006 pramipexole and ropinirole became the first pharmaceuticals approved for the treatment of moderate to severe idiopathic RLS in Europe and the US. Prior to this, a variety of drugs not approved for this indication were used to treat the symptoms of this disorder. The present authors aimed to analyze the patterns of treatment of RLS in the primary care setting from 1990–2004, examine the efficacy of these treatments, and the associated use of healthcare resources.

A sample of 14 716 patients with primary or secondary RLS was identified from the UK General Practice Research Database (GPRD), an anonymous database of patient records from UK general practices that use the same clinical software. The analysis focused on a sample of 8621 of these patients who had been registered with their GP for at least 2 years before their diagnosis of RLS. Each of these cases was matched by age, sex, general practice, and date of registering with the general practice with 10 control subjects who did not have a diagnosis of RLS, making up a control cohort of 85 087 individuals. Each group consisted of 73% females.

During the study period, the annual incidence of RLS diagnoses increased from 4.6 per 10 000 person-years in 1990 to 6.1 per 10 000 person-years in 2004. Rates of hypertension, diabetes, and depression were significantly higher in the RLS group compared with the control group. Prescribing rates of both sleep and antidepressant medications remained constant for the control group throughout the study period. However, in the RLS group, the frequency of prescriptions for sleep medication was higher after the diagnosis of RLS, increasing from 19.8% 2 years prior to their diagnosis to 27.4% in the year afterwards, then decreasing to 25.2%; the prescribing rates of antidepressants followed similar trends. Compared with the control group, the RLS group initially had a higher frequency of prescriptions written, referrals to specialists, and laboratory tests, and these continued to increase during the study period.

It is interesting to see an increase in the rate of diagnosis of this condition, which may reflect a rise in awareness.

However, the increased use of medications and referrals before diagnosis indicates that patients were investigated for several conditions before a diagnosis of RLS was made. The authors conclude that medications not approved for the treatment of RLS are not associated with a reduction in clinical symptoms or use of healthcare resources.

Address for reprints: C Martinez, Department of Medicine, Faculty of Medicine, McGill University, 3775 University Street, Montreal, Canada. Email: carlos.martinez@clinepi.mcgill.ca

Restless legs symptoms without periodic limb movements in sleep and without response to dopaminergic agents: a restless legs-like syndrome?

Baumann CR, Marti I, Bassetti CL.
Eur J Neurol 2007;**14**:1369–72.

The authors of this study characterized a subset of patients with restless legs syndrome (RLS) who lack periodic limb movements in sleep and who do not exhibit a favorable response to dopaminergic therapy. In comparison with "classical" RLS patients, this subset was found to be of a significantly younger age, have more severe symptoms, and harbor greater psychiatric comorbidities.

Patients must meet essential criteria to be diagnosed with restless legs syndrome (RLS), namely the presence of an urge to move the legs that is alleviated with movement and worsens during rest, especially during the evening time. Other characteristics, such as family members affected by RLS, an adequate response to dopaminergic therapy, and the presence of periodic limb movements during sleep (PLMS) or wakefulness, are used to support the identification of RLS and occur in approximately 80% of patients, but are not required for the actual diagnosis. The present authors aimed to identify and characterize a subset of "RLS-like" patients who meet the essential criteria for RLS but, unlike patients with "classical" RLS, neither have PLMS nor respond to dopaminergic therapy.

Patients were classified as having classical RLS if they had either a symptomatic improvement of ≥10 points on the International RLS Study Group Rating Scale (IRLS) with dopaminergic therapy or a PLMS index of >15/h, as determined by polysomnography (PSG). Due to the retrospective nature of the study, a PSG evaluation of PLMS was not available for all participants – only those without a response to dopaminergic therapy. Therefore, the authors were able to identify the absence of both these criteria using the available data and classify such patients as RLS-like, but were unable to determine the presence of both symptoms.

The study comprised a consecutive series of 117 patients (59 women and 58 men with a mean age of 59±14 years), all of whom met the essential criteria for RLS but were without other sleep–wake disturbances. The analysis revealed that 103 patients (88%) had classical RLS, while 14 had RLS-like symptoms. The latter group was younger than those with classical RLS, their symptoms more severe and experienced for a shorter duration, and they had a higher prevalence of psychiatric diagnoses (p=0.001).

The authors speculate that the RLS-like patients may represent a distinct subset with a specific etiological and pathological profile. Their data are supported by a previous study that found an association between the presence of a specific genetic sequence and PLMS [1], which was only evident in RLS patients with PLMS, and not in those without. Further studies of the genetic basis of RLS may provide insight into whether different genetic pathways are involved in the development of the different subtypes of this syndrome. Limitations of the study include the small cohort of RLS-like patients, the lack of PSG evaluation of all patients, and the potential under-diagnosis of psychiatric ailments as not all patients were examined by a psychiatrist.

1. Winkleman J, Schormair B, Lichtner P et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nature Genetics* 2007;**39**:10000–6.

Address for reprints: CL Bassetti, Department of Neurology, University Hospital Zurich, Frauenklinikstrusse 26, CH-8091 Zurich, Switzerland. Email: claudi.bassetti@usz.ch

INSOMNIA

Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Krystal AD, Erman M, Zammit GK et al; ZOLONG Study Group.
Sleep 2008;**31**:79–90.

The present authors examined the long-term efficacy and tolerability of a zolpidem extended-release formulation in adults with chronic primary insomnia who had difficulties with both sleep onset and sleep maintenance. At week 12 of the treatment, a statistically significant improvement in sleep symptoms was reported by 89.8% of patients in the zolpidem extended-release group compared with 51.4% of the placebo group. At week 24, a favorable response was reported by 92.3% and 59.7% of the respective treatment groups, confirming the long-term efficacy of the zolpidem extended-release formulation.

Subjects with chronic insomnia often report symptoms for many years and thus many chronic insomnia patients take sedative–hypnotics for long periods of time. Zolpidem tartrate binds to the α-1 subunit subtype of the γ-aminobutyric acid receptor, and is indicated for the short-term treatment of insomnia. It is characterized by a relatively short half-life (2.5 h) and therefore reduces the latency to persistent sleep and increases total sleep time, but is not consistently efficacious for the treatment of sleep maintenance symptoms that occur in the majority of insomnia patients. Zolpidem extended-release 12.5 mg formulation has been developed to extend the duration of action of the original formulation. It is a dual-layered tablet that allows a biphasic release of the drug – an initial release to facilitate sleep onset, and a delayed release to benefit sleep maintenance throughout the night. In a short-term, placebo-controlled study in adult patients with primary insomnia, the zolpidem extended-release formulation significantly improved sleep onset and sleep maintenance measures on the first 2 nights of treatment and after 2 weeks of treatment [1].

The present national, multicenter, Phase IIIb, randomized, double-blind, placebo-controlled 26-week study examined the long-term efficacy of zolpidem extended-release, self-administered for between 3 and 7 nights per week for 24 weeks, in adults with chronic primary insomnia who exhibited difficulties with both sleep onset and sleep maintenance. The safety and tolerability, and effects of abrupt discontinuation of the formulation were also examined.

Subjects aged 18–64 years who met criteria for chronic primary insomnia from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) were eligible for inclusion. Of 1701 patients were screened for inclusion during the first 7 days of the study, a total of 669 received zolpidem extended-release and 349 received placebo during the double-blind treatment phase (24 weeks). Baseline characteristics were similar in the two treatment groups.

The primary efficacy outcome was the score on the Patient's Global Impression (PGI) item 1 (treatment aid to sleep), assessed at week 12 of the treatment period in the intent-to-treat population. A total of 436 patients (64.7%) in the zolpidem extended-release group completed the study treatment period, with "patient's request" being the most frequently cited reason for discontinuation. In the placebo group, 184 patients (52.4%) completed the study treatment period, with "lack of efficacy/disease progression" cited as the most frequent reason for discontinuation (in 82 patients) within this group.

Scores on PGI item 1 at week 12 in the zolpidem extended-release group were significantly superior to those in the placebo group, with 89.8% of patients in the zolpidem extended-release group reporting that the medication helped them sleep, compared with 51.4% in the placebo group ($p<0.0001$). At week 24, a favorable response was reported by 92.3% and 59.7% of the zolpidem extended-release and placebo groups, respectively. The zolpidem extended-release formulation was also statistically superior to placebo on other patient and clinician-rated assessments of sleep.

The most frequent adverse events in zolpidem extended-release recipients were headache, anxiety, and somnolence. No rebound effect was observed during the first 3 nights of discontinuation, assessed during the final week of the 26-week study.

Although this study is limited by the absence of polysomnography-evaluated sleep assessments and the lack of an active control group, the findings confirm the efficacy and tolerability of 3 to 7 nights/week dosing of zolpidem extended-release 12.5 mg for up to 6 months in patients with insomnia, with improvements in sleep onset and sleep maintenance.

1. Roth T, Soubrane C, Titeux L et al. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. *Sleep Med* 2006;**7**:397–406.

Address for reprints: AD Krystal, Box 3309, Duke University Medical Center, Durham, NC 27710, USA. Email: kryst001@mc.duke.edu

Evaluation of automated and semi-automated scoring of polysomnographic recordings from a clinical trial using zolpidem in the treatment of insomnia

Svetnik V, Ma J, Soper KA et al.
Sleep 2007;**30**:1562–74.

The authors of this study compared manual scoring of polysomnograms with two different automated scoring systems using different degrees of manual review. Agreement between automated and manual scoring was approximately 70%, and this increased with manual review of the automated results.

The development of automated procedures for scoring the polysomnogram would be of great benefit in terms of cost and standardization. In this study, Svetnik et al. compared six methods of polysomnographic scoring, all of which were based on Rechtschaffen and Kales scoring criteria [1]:

- Manual scoring.
- Automated scoring by Morpheus (Widemed Ltd, Herzliya, Israel).
- Automated scoring by Somnlyzer 24×7 (The Siesta Group Schlafanalyse GmbH, Vienna, Austria).

- Automated scoring by Morpheus with full manual review.
- Automated scoring by Morpheus with partial manual review.
- Automated scoring by Somnolyzer 24×7 with partial manual review.

The comparison was carried out on 164 polysomnograms obtained from 82 subjects during 2 nights of sleep. Placebo was administered 30 min before bedtime on one night while zolpidem (10 mg) was taken on the other.

Agreement was 70–72% when comparing fully automated scoring with manual scoring; this is within the range previously reported for intersite agreement between manual scorers (71–77%) [2–4]. As expected, manual review increased the agreement of automated scoring with manual scoring. The treatment effect sizes (the differences between the indices resulting from scoring on zolpidem vs. placebo nights) approached those of manual scoring with full manual review of Morpheus scoring.

The authors conclude that automated scoring with manual review may be needed to produce optimal results. While this will not reduce costs, it might increase intersite reproducibility of results, and the authors suggest that studies should be conducted to determine whether this is the case.

1. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Los Angeles: Brain Information Service, 1968.
2. Norman RG, Pal I, Stewart C et al. Interobserver agreement among sleep scorers from different centers in a large data set. *Sleep* 2000;**23**:901–8.
3. Collop NA. Scoring variability between polysomnography technologists in different sleep laboratories. *Sleep Med* 2002;**3**:43–7.
4. Danker-Hopfe H, Kunz D, Gruber G et al. Interrater reliability between scorers from eight European sleep laboratories in subjects with different sleep disorders. *J Sleep Res* 2004;**13**:63–9.

Address for reprints: V Svetnik, Merck Research Laboratories, Biometrics Research, Rahway, NJ 07065, USA. Email: vladimir_svetnik@merck.com

The subjective meaning of sleep quality: a comparison of individuals with and without insomnia.

Harvey AG, Stinson K, Whitaker KL et al.
Sleep 2008;**31**:383–93.

Sleep quality is an inadequately defined subjective construct, implicated in the classification of chronic insomnia and associated with a variety of positive upshots of day-to-day life. This aim of this study was to examine the subjective interpretation of sleep quality in individuals suffering from insomnia compared with that reported by normal sleepers. Results showed that patients with insomnia and normal sleepers alike reported broadly similar meanings of sleep quality. The study also unearthed new variables, not previously mentioned in the existing literature, used by subjects to define sleep quality.

Despite its widespread use, the term sleep quality has yet to be systematically described. In an attempt to define the meaning of sleep quality this study looked at the importance of different variables used in its classification found in the existing literature. The authors also shed light on new variables considered significant by the subjects. In this exploratory, cross-sectional investigation, the authors compare the reports of individuals with insomnia with normal sleepers, in contrast with previous studies that have mainly focused only on normal sleepers.

The insomnia group was made up of 25 subjects who met criteria for primary insomnia on the Insomnia Diagnostic Interview (IDI) with problems present for at least 3 nights per week for the previous month. The normal sleep group comprised 28 individuals who failed to meet the IDI criteria and scored ≤7 on the insomnia scale.

Three techniques were used to elicit the meaning of sleep quality. The "Speak Freely" procedure analyzed the participants' descriptions of good and poor sleep quality nights, attributing percentages to each variable mentioned. The second method, the Sleep Quality Interview, involved asking the subjects to grade different criteria for judging sleep quality. Finally, a 7-day sleep diary was used to record the frequency with which patients mentioned each variable.

The meaning of sleep quality among insomniacs was found to be largely similar to that for normal sleepers, with subjective feelings experienced the following day appearing to be the most important foundation for judging sleep quality. All three methods found "tiredness on waking and throughout the day", "feeling rested and restored on waking", and "number of wakings" the most commonly associated with forming a judgment on sleep quality. The main disparity found between groups was that the insomnia group rated most of the variables in the Sleep Quality Interview as of greater importance when judging sleep quality than normal sleepers.

The Speak Freely procedure highlighted a number of variables among the insomnia group that have not previously appeared in the literature, for example: "coping behaviors" and "time of waking". The sleep diaries brought forth novel variables such as "time of waking" and "body sensations at night".

Due to the nature of the study involving multiple comparisons of data, concern exists as to the presence of type 1 error. Further investigations should be performed to investigate the nature of these variables and determine whether they are *bona fide* indicators of sleep quality or a consequence of a psychological bias misinterpreting ambiguous information.

Address for reprints: AG Harvey, Department of Psychology, University of California, Berkeley, CA 94720-1650, USA

Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design

Ouellet M, Morin CM.
Arch Phys Med Rehabil 2007;**88**:1581–92.

This single-case, multiple baseline study of cognitive–behavioral therapy for subjects with insomnia following traumatic brain injury reports statistically significant improvements in sleep and fatigue that were still evident at the 3-month post-treatment follow-up.

Sleep difficulties commonly occur after traumatic brain injury (TBI). It has been reported that symptoms of insomnia occur in 30–70% of cases [1,2], and about 30% meet insomnia diagnostic criteria [3,4]. In many cases insomnia develops into a chronic condition. However, there is a near complete absence of research on the treatment of insomnia occurring in this setting. There have been no controlled trials and only one study of open-label treatment with zopiclone or lorazepam in six patients [5]. This paper reports the results of a single-case, multiple baseline study of 8 weeks of cognitive–behavioral therapy (CBT) for insomnia after TBI in 11 subjects. The therapy included sleep restriction, cognitive restructuring, and sleep hygiene; CBT is a reasonable treatment option because it is free of the potential interactions with neurological impairments associated with medication therapy.

At treatment end, there were statistically significant improvements compared with baseline in total wake time (59.29±39.54 vs. 128.46±47.86 min; $p<0.017$) and sleep efficiency (87.99±7.99 vs. 77.2±8.76; $p<0.017$), and these were accompanied by a statistically significant decrease in fatigue assessed using the Multidimensional Fatigue Inventory (55.89±12.65 vs. 63.45±.9.25; $p<0.017$). These therapeutic benefits were maintained throughout the 3-month post-treatment follow-up period.

These findings indicate the potential utility of CBT for the treatment of insomnia occurring in individuals after TBI. They also highlight the need for more studies on the treatment of insomnia in this patient population.

1. Beetar JT, Guilmette TJ, Sparadeo FR. Sleep and pain complaints in symptomatic traumatic brain injury and neurologia populations. *Arch Phys Med Rehabil* 1996;**77**:1298–302.
2. Cohen M, Oksenberg A, Snir D et al. Temporally related changes of sleep complaints in traumatic brain injured patients. *J Neurol Neurosurg Psychiatry* 1992;**55**:313–5.
3. Fichtenberg NL, Zafonte RD, Putnam S et al. Insomnia in a post-acute brain injury sample. *Brain Inj* 2002;**16**:197–206.
4. Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia after traumatic brain injury: frequency, characteristics, and risk factors. *J Head Trauma Rehabil* 2006;**21**:199–212.
5. Li Pi Shan RS, Ashworth NL. Comparison of lorazepam and zopiclone for insomnia in patients with stroke and brain injury: a randomized, crossover, double-blinded trial. *Am J Phys Med Rehabil* 2004;**83**:421–7.

Address for reprints: MC Ouellet, Recherche en Traumatologie et Médecine d'Urgence Hopital de l'Enfant-Jésus du CHA 1401, 18e Rue, QC G1J 1Z4, Canada. Email: marie-christine.ouellet@mail.mcgill.ca

EXCESSIVE DAYTIME SLEEPINESS

Placebo and modafinil effect on sleepiness in obstructive sleep apnea

Bittencourt LRA, Lucchesi LM, Rueda AD et al.
Prog Neuropsychopharmacol Biol Psychiatry 2008;**32**:552–9.

The authors aimed to identify the effect of placebo response in this trial of 22 patients with obstructive sleep apnea, treated with continuous positive airway pressure, but who still suffered excessive daytime sleepiness (EDS). The results showed that modafinil is an effective treatment for the symptoms of EDS, and suggest that a similar protocol should be considered in other drugs trials measuring outcomes based on subjective response.

Obstructive sleep apnea (OSA) is estimated to affect 2–4% of middle-aged adults. The sleep fragmentation resulting from microarousals occurring during OSA causes sleep disruption and excessive daytime sleepiness (EDS). This can persist, even in those adequately treated with CPAP.

Modafinil has shown benefit in patients with EDS; however, some trials have reported these benefits only in objective tests, some only in subjective tests, and others in both cases. The study authors therefore sought to assess whether a placebo effect persisted in these patients after randomization, thereby causing the differing findings that have been reported.

Twenty-two patients with OSA who were currently receiving CPAP treatment were enrolled in the study. All patients had an Epworth Sleepiness Score (ESS) >10. Subjects received blinded placebo treatment for 7 days and were then randomized to receive either placebo (n=11) or modafinil (300 mg/day; n=9) for a further 21 days. Patients were evaluated at baseline, randomization, and study end using the ESS, maintenance of wakefulness test, and Short-Form 36, among others.

Comparison of the two groups revealed that although ESS scores did not change during the placebo period in those in the modafinil group, those in the placebo group experienced a significant reduction in ESS scores (14.2 to 9; $p=0.05$) during the first 7 days of placebo treatment, although this did not continue during the second placebo treatment period. In contrast, those in the modafinil group experienced a significant reduction during the 21-day modafinil treatment period (ESS score 15.2 to 7.8; $p=0.0006$). Three patients in the modafinil and nine patients in the placebo group were classed as placebo responsive.

The authors conclude that modafinil, used adjunctive with CPAP therapy, improves EDS in patients suffering from OSA.

They highlight the importance of including a blinded placebo period prior to randomization to fully observe the placebo effect, and suggest that a similar process should be performed in other drug trials that are based on measures of subjective response.

Address for reprints: L Bittencourt , Sleep Medicine and Biology Discipline, Psychobiology Department, Universidade Federal de São Paulo, Napoleão de Barros 925, São Paulo 04024-002, SP Brazil. Email: lia@psicobio.epm.br

Patient-management strategies

Thorpy MJ, Lieberman JA 3rd, Roth T et al.
Am J Manag Care 2007;**13**(6 Suppl):S140–7.

In this article, the authors describe excessive daytime sleepiness (EDS) as a common problem with a range of adverse effects. These consequences are reviewed and both non-pharmacological and pharmacological interventions to reduce EDS and its associated adverse outcomes are discussed. A case study is provided.

The present authors identify excessive daytime sleepiness (EDS) as a common and serious problem that can lead to cognitive impairment, psychomotor disturbances, and impaired social functioning. They report that EDS is associated with impaired occupational performance, including medical errors by interns and occupational injuries in shift workers, and with motor vehicle accidents.

Furthermore, the authors report that conditions producing EDS (e.g. restricted sleep time, obstructive sleep apnea [OSA]) contribute to diabetes, cardiovascular disease, and other comorbidities. They emphasize that EDS can hamper the implementation and effectiveness of medical interventions.

To assess EDS and the sleep disorders that might account for it, the authors recommend using the Epworth Sleepiness Scale, sleep diaries, and bed partner reports of patients' breathing during sleep. If sleep diaries do not reveal a reason for EDS (e.g. insufficient night-time sleep, circadian rhythm disorder), the authors suggest use of more sophisticated sleep assessment methods, such as formal sleep studies. An algorithm is provided to aid in assessment of causes of EDS. They report that laboratory tests of thyroid function might be useful when sleep apnea is considered, and that ferritin levels should be measured when restless legs syndrome is suspected.

Regarding non-pharmacological interventions for sleep, the authors recommend sleep hygiene, bright light exposure, and behavioral interventions (e.g. cognitive–behavioral therapy, stimulus control, sleep restriction, relaxation techniques). They describe continuous positive airway pressure, oral devices, and surgery as interventions for OSA.

Pharmacological approaches for treating EDS are described, including stimulant medications (e.g. modafinil) and hypnotics for EDS due to insomnia (e.g. sedating antidepressants, benzodiazepines, non-benzodiazepine hypnotics). They emphasize that polysomnography is necessary in cases of suspected OSA (e.g. drowsy driving) and that primary care physicians should refer to sleep specialists when the cause of EDS is unclear or the physician is unable to competently treat the sleep disturbance.

Address for reprints: MJ Thorpy, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, USA. Email: thorpy@aecom.yu.edu

Evaluation of the safety of modafinil for treatment of excessive sleepiness

Roth T, Schwartz JR, Hirshkowitz M et al.
J Clin Sleep Med 2007;**3**:595–602.

Modafinil has been shown to be effective at reducing excessive daytime sleepiness experienced by patients with shift-work sleep disorder, obstructive sleep apnea, and narcolepsy in six randomized studies. The present authors reviewed the safety profile of this wake-promoting agent using data from these trials. They found modafinil to be well-tolerated with very low rates of adverse events, 90% of which were mild or moderate.

Excessive daytime sleepiness (EDS) is a complaint estimated to affect one-third of the general population, and is a common symptom of shift-work sleep disorder (SWSD), obstructive sleep apnea (OSA), and narcolepsy. Modafinil is a wake-promoting agent that has been shown to effectively reduce EDS in patients with these disorders.

The study authors reviewed the toxicity profile of modafinil in six trials that had been performed to assess the efficacy of this drug in the treatment of EDS. All studies were randomized, placebo-controlled, and double-blinded. Patients included were ≥18 years of age and met the standard diagnostic criteria for SWSD, OSA, or narcolepsy, with no other cause of EDS.

In total, the trials included 273 subjects with SWSD, 292 with OSA, and 369 with narcolepsy – who were taking modafinil at a dose of 200 mg, 300 mg, or 400 mg daily – and 567 individuals receiving placebo. In addition to the recording of adverse events, the subjects' blood pressure, heart rate, body weight, electrocardiogram intervals, and polysomnography results were monitored during the study periods. Data were analyzed for all trials together as well as according to the type of sleep disorder and dose of modafinil.

The overall discontinuation rates were similar for active treatment and placebo arms (18% vs. 16%, respectively),

with discontinuation due to adverse events occurring in 8.2% of those in the treatment arm, and 2.8% of the placebo group. Overall, 90% of the adverse events were mild or moderate and occurred within the first 4 weeks of treatment. The most commonly reported adverse event was headache, which was the only adverse event to occur in a dose–response relationship; 32% of the subjects receiving 200 mg of modafinil reported headache, 26% of those receiving 300 mg, and 40% receiving 400 mg ($p<0.05$ vs. placebo). The next most common adverse events were nausea, which affected 11% of the modafinil group and 3% of the placebo group, and infection, reported by 10% of the modafinil group and 12% of the control group. There were 18 serious adverse events in the 934 subjects who received modafinil and nine in the 567 individuals who were given placebo. Changes in vital signs and electrocardiogram results after treatment were rare in both groups.

Modafinil was shown to be well tolerated by individuals with EDS caused by SWSD, OSA, or narcolepsy. The authors suggest that modafinil's favorable safety profile may be due to the drug's selectivity for sleep–wake centers in the brain, rather than using widespread dopaminergic pathways. Although none of the trials assessed included a long-term follow-up period, the authors note that modafinil treatment has been associated with a similar safety profile in two long-term studies of patients with narcolepsy.

Address for reprints: T Roth, Henry Ford Sleep Disorders Center, 277 West Grand Boulevard, Detroit, MI 48202, USA. Email: TRoth1@hfhs.org

CIRCADIAN RHYTHM

Reduced nitric oxide causes age-associated impairment of circadian rhythmicity

Kunieda T, Minamino T, Miura K et al.
Circ Res 2008;**102**:607–14.

The relationship between circadian rhythmicity and aging is explored in the present article with a particular focus on the role of nitric oxide (NO), production of which is known to decrease with age. Treatment of elderly mice with existing circadian impairments using an NO donor led to significant improvements in circadian rhythmicity. This study demonstrates the protective role of NO treatment against alterations in circadian rhythmicity associated with aging, and provides an attractive target for the development of future therapies.

Previous studies have established a clear relationship between aging and impaired circadian rhythmicity [1]. Such impairment has been implicated as a causative factor in age-related complications such as atherosclerosis and hypertension.

The production of nitric oxide (NO) – an established regulator of cardiovascular homeostasis – is known to decline with age. This results in the dysregulation of the transcriptional cascade involved in the activation of the "*Clock*" gene, which in turn directly control circadian rhythmicity.

The authors of the present study investigated a possible protective role of NO against the age-related alterations in circadian rhythm and concomitant cardiovascular complications in elderly subjects. The authors found that elderly mice with impaired circadian rhythmicity had limited NO production, and that treatment with an NO donor resulted in significant improvements to circadian impairments. Conversely, inhibition of NO synthase (NOS), the enzyme responsible for NO production, led to impairment of *Clock* gene expression with detrimental effects to circadian variation in blood pressure, a finding that clearly has implications in terms of hypertensive complications.

The present study highlights the integral role played by NO in cardiovascular homeostasis. This twinned with the identification of reduced NOS activity and thus reduced NO in the elderly, provides a promising target for the future treatment of impaired circadian rhythmicity in relation to cardiovascular disease

1. Weinert D. Age-dependent changes of the circadian system. *Chronobiol Int* 2000;**17**:261–83.

Address for reprints: I Komuro, Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan.
Email: komuro-tky@umin.ac.jp

Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine Report

Morganthaler TI, Lee-Chiong T, Alessi C et al.
Sleep 2007;**30**:1445–59.

The American Academy of Sleep Medicine Standards of Practice Committee carried out a review of the available literature and in this paper present a set of practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. This article provides a valuable addition to the literature for any practitioner involved in the clinical management of these disorders.

There has been great progress in research on the biology of the circadian rhythm; however, the treatment of disorders of circadian rhythm in clinical practice has not kept pace with this rapid rate of growth. As a result, the American Academy of Sleep Medicine Standards of Practice Committee carried out a review of the available literature and used their

findings to develop a set of practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders, consisting of shift-work disorder (SWD), jet lag disorder (JLD), advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), irregular sleep–wake rhythm (ISWR), and free-running disorder (FRD). A set of diagnostic tools is discussed, including sleep logs, actigraphy, the Morningness–Eveningness Questionnaire (MEQ), circadian phase markers, and polysomnography (PSG), together with treatments such as planned sleep schedules, timed light exposure, timed melatonin doses, hypnotics, stimulants, and alerting agents. The authors provide recommendations as to the use of each diagnostic tool and treatment for each of the disorders on a scale from "option" to "guideline".

In terms of diagnostic tools, the use of actigraphy when a circadian rhythm disorder is suspected is rated as a "guideline". The use of actigraphy for diagnosis varies from "option" to "guideline" depending on the suspected disorder. PSG is recommended only to rule out other sleep disorders. Insufficient evidence supports the use of the MEQ for routine use (rated as "option"). Circadian phase markers are recommended only for diagnosis of FRD. Actigraphy is recommended as a "guideline" for use as a treatment outcome measure.

Among the treatment options, planned sleep schedule is recommended (rated as a "standard") for SWD, JLD, DSPD, ASPD, and ISWR. Timed light exposure is not recommended (rated as "option") owing to variable reported success. Timed melatonin is recommended ("standard") for JLD and, in unsighted persons, as a "guideline" for SWD, DSPD, and FRD. Hypnotic medications are recommended as a "guideline" for night shift workers. Stimulants are considered to be an "option" for JLD and SWD, while modafinil is indicated for use during the night shift for SWD ("guideline").

These practice parameters provide a significant contribution to improving the clinical management of disorders of circadian rhythm.

Address for reprints: Standards of Practice Committee, American Academy of Sleep Medicine, 1 Westbrook Corporate Center, Suite 920, Westchester, IL 60154, USA. Email: aasm@aasmnet.org

MISCELLANEOUS

Longitudinal study of bad dreams in preschool-aged children: prevalence, demographic correlates, risk and protective factors

Simard V, Nielsen TA, Tremblay RE et al.
Sleep 2008;**31**:62–70.

This was the first study to examine the occurrence of bad dreams in such a young group of children. The authors found that bad dreams occurred less frequently than they expected and appeared to be a stable characteristic. Results from this study warrant further examination of bad dreams in preschool aged children.

Although bad dreams are thought to be common during early childhood, research regarding this topic is rare. Most studies of the prevalence of bad dreams in pediatric populations have focused on children aged ≥5 years. The present authors examined the prevalence, potential reasons for, and significance of bad dreams in preschool-aged children. They hypothesized that the following factors would be associated with bad dreams:

- Parental sleep-facilitating behaviors that favor dependence rather than autonomy, such as cuddling while falling asleep and physical comforting when awake at night.
- Pathological symptoms such as psychological distress, anxiety, and depression.
- Separation anxiety.
- Difficult temperament.

In all, 1997 children from the Quebec Longitudinal Study of Child Development participated up to the first endpoint of the study (29 months), with 1434 participating throughout the study period until the final 6 year follow-up examination. Assessment comprised the Self-Administered Questionnaire for the Mother, in general provided by the biological mother

Bad dreams were reported to be a relatively rare occurrences in children aged between 29 months and 6 years, with between 1.7% and 3.9% of respondents reporting that bad dreams occurred always or often. The results showed that the presence of bad dreams is a relatively stable characteristic and becomes more so over time. This may indicate that these dreams will continue into adolescence and adulthood and, therefore, that children may benefit from early intervention. Despite studies of older children indicating a higher prevalence of bad dream amongst girls, particularly in adolescence, this study did not find any gender-related differences in the prevalence of bad dreams among preschool aged children. High family income, absence of siblings at 29 months, and a non-immigrant mother were all associated with bad dreams. Parental nurturing after awakening was associated with bad dreams at the 29- and 41-month assessments, as was sleep onset nurturance at 29 months, a difficult temperament at 5 months, and anxiousness at 17 months.

Bad dreams occur less frequently in preschool aged children than the authors expected. As the occurrence of bad dreams seemed to be a trait-like characteristic, it is possible that early intervention could prevent these from occurring at a later stage in their lives. However, as this trial was the first study examining these parameters in such young children, the results will need to be confirmed in further investigations.

Address for reprints: TA Nielsen, Centre d'etude du sommeil, Hôpital du Sacré-Coeur de Montréal, QC, Canada.
Email: tore.nielsen@umontreal.ca

When sleep is perceived as wakefulness: an experimental study on state perception during physiological sleep

Weigand D, Michael L, Schulz H.
J Sleep Res 2007;**16**:346–53.

Previous studies on sleep–wake misperception have confirmed that a subject's accuracy in identifying an arousal relies on the stage of sleep he or she is in at the time of the arousal, with rapid eye movement (REM) sleep being the most accurate. The current authors collected data from individuals in stage two and REM sleep subjected to deliberate awakenings.

Studies on sleep–wake misperception, or paradoxical insomnia as it is now referred to according to the second edition of the International Classification of Sleep Disorders, have investigated several aspects of the perception of sleep. Many of these past studies have focused on a subject's ability to identify an arousal, either deliberate or spontaneous, by pressing a button. These studies have confirmed that accuracy relies on the stage of sleep a subject is in at the time of the arousal, with rapid eye movement (REM) sleep being the most accurate. The current authors collected data on deliberate awakenings from randomized subjects in stage two and REM sleep.

Polysomnography (PSG) and nocturnal interviews were carried out for 68 subjects without a sleep complaint (mean age 24.1 years, 43 female) who were considered "good sleepers". A standardized audio signal (70 dB/400 Hz) was used to awaken subjects in either stage two or REM sleep. The nocturnal interview determined whether the subject thought they were awake or asleep before the tone and how sure they felt about their answer, as well as how deeply they had been sleeping prior to hearing the tone. The interview also inquired about thoughts, clarity of thoughts, and awareness, including control of thoughts.

Overall, 29.4% of the subjects reported being awake before the audio signal was given while electrophysiologically they were asleep. Furthermore, the results indicated that no significance was detected in the level of certainty of awake judgments between stage two and REM sleep. Further investigation into the nocturnal interview showed that subjects who answered "yes" to having something on their mind before being awakened were more likely to be in REM rather than stage two sleep ($p<0.05$). These subjects also reported clearer and more image-like content. However, subjects reported a low level of controllability of their thoughts regardless of sleep stage. PSG variables (sleep latency, sleep efficiency, percent of stage one, two, slow-wave, and REM sleep) did not differ among participants.

Although this study has several limitations, the results are similar to previous data suggesting that some good sleepers perceive their sleep as wakefulness. These data suggest there is a need for future studies to explore the cognitive processes during sleep and how they contribute to sleep state perception.

Address for reprints: D Weigand, George-August-Universität Göttingen, George-Elias-Müller-Institut für Psychologie, Gosslerstrasse 14, 37073 Göttingen, Gemany. Email: weigand@psych.uni-goettingen.de

MEETING REPORT

Sleep Medicine 2008

Scottsdale, AZ, USA, January 10–13, 2008

Brian Boehlecke, MD, MSPH

University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Sleep Medicine 2008 was sponsored by the American College of Chest Physicians (ACCP) and the ACCP Sleep Institute. A hands-on polysomnography (PSG) workshop and 29 lectures covering current concepts of diagnosis and treatment in sleep medicine were presented by 17 faculty members. In addition to the content areas addressed in last year's conference, presentations were given on the future direction of sleep medicine, complex sleep apnea, sleep in patients with pulmonary diseases, mechanisms of sleep apnea, and parasomnias.

The future of sleep medicine

Barbara Phillips (University of Kentucky Medical Center, Lexington, KY, USA) presented her thoughts on several issues affecting the future of sleep medicine. The prevalence of obstructive sleep apnea (OSA) is likely to continue to increase due to the lengthening lifespan and increasing incidence of obesity in the general population [1]. Efficient identification and treatment is imperative, because of the increasing numbers afflicted and the significant morbidity and mortality associated with untreated OSA [2,3]. Dr Phillips believes there is a need for change in the current usual management algorithm of in-laboratory sleep studies for definitive diagnosis and continuous positive airway pressure (CPAP) titration prior to initiating therapy. She feels that portable monitoring should be used to diagnose those with a high prior probability of OSA. The US Centers for Medicare and Medicaid Services has issued a proposal to allow portable monitoring as a covered diagnostic service for its enrollees. Dr Phillips stated that in-laboratory studies are still indicated for those patients with coexisting pulmonary disease, sleep disorders other than OSA, or negative portable monitoring results despite a high prior probability of OSA, as well as OSA patients who do not respond as expected to CPAP therapy.

Furthermore, Dr Phillips indicated that she believes in-laboratory CPAP titration is not necessary for adequate management of most patients with uncomplicated OSA. She argued that home use of autotitrating positive airway pressure devices can be used to manage these patients with equivalent clinical outcomes to in-laboratory titration studies [4,5]. Her prediction is that most OSA will be managed by primary care providers and that many subspecialty physicians, such as cardiologists, geriatricians, and obstetrician–gynecologists, will increasingly become directly involved with the management of OSA in their patients.

Mechanisms of sleep apnea

Brian Boehlecke (University of North Carolina, Chapel Hill, NC, USA) discussed current concepts of the mechanisms of OSA. The caliber of the lumen of the collapsible segments of the upper airway is determined by anatomical factors, such as the size of the tongue and tonsils, the balance between collapsing and dilating forces acting on the wall, and the wall's intrinsic "stiffness" [6,7].

Obesity, especially of the central type, is recognized as a major risk factor for OSA. Fat deposition in the soft tissues of the neck increases tissue pressure, tending to collapse the upper airway. This may explain the closer association of OSA with neck circumference (and waist–hip ratio) than with overall body mass index. However, an increased prevalence of bony craniofacial abnormalities resulting in a smaller lumen may predispose certain ethnic groups (e.g. Japanese) to OSA in the absence of obesity [8].

A component of upper airway wall "stiffness" is tonic contraction of wall muscles. The magnitude of this tonic activation is higher during wakefulness than during non-rapid eye movement (REM) sleep. The onset of sleep removes this "wakefulness stimulus" and reduces the ability of the airway to resist collapsing forces [9]. During wakefulness, OSA patients manifest increased tonic activation of the airway muscles compared with healthy persons. This appears to offset the increased collapsing forces from peri-airway fat and soft tissue. However, in OSA patients the onset of sleep causes a greater reduction in this tonic activation than in healthy persons, thus contributing to an increased likelihood of airway collapse [10].

Activation of the genioglossus (GG) muscle pulls the tongue forward and is an important component of the

forces that maintain patency of the upper airway. The impulses emanating from the central nervous system (CNS) that activate the GG have been found to have a phasic component that increases just before the start of each inspiration. The magnitude of this activation appears to be reflexively modulated by feedback from sensory nerves which detect negative intraluminal pressure [11]. In OSA patients the magnitude of this phasic activation is reduced. In addition, there is some evidence that the upper airway muscles of OSA patients are weaker than normal, possibly due to damage from vibration during years of nocturnal snoring predating the development of frank apneic events [12]. Thus, a combination of anatomical and neuromuscular abnormalities of the upper airway usually underlies the development of OSA.

Respiratory control mechanisms may also play a role in OSA. The apnea threshold, the $PaCO_2$ level at which neural drive to respiration ceases, is usually only slightly (2–6 mmHg) below the normal eucapneic sleeping $PaCO_2$. If the $PaCO_2$ level drops below this threshold, a "central" apnea occurs. Some patients with OSA are more easily aroused by the increased respiratory drive induced by a rise in $PaCO_2$, i.e. they have a reduced "arousal threshold". If the increased ventilation that occurs in response to the rise in $PaCO_2$ after an obstructive hypopnea or apnea stimulates an arousal, the resumption of the wakefulness stimulus will further increase the ventilatory response and may lower the $PaCO_2$ level below the apnea threshold causing a central apnea. Obesity causes a low end-expiratory lung volume especially when supine. This causes a greater reduction in $PaCO_2$ for a given reduction in ventilation. Hypoxemia increases the ventilatory response to the increase in $PaCO_2$ after a hypopnea or apnea, which then predisposes to a subsequent ventilatory "overshoot" with reduction of the $PaCO_2$ level below the apnea threshold. In addition, some patients with severe OSA have been shown to have a higher intrinsic ventilatory response to elevations in $PaCO_2$ than those with milder OSA [13]. Thus patients with OSA may be predisposed to central apneas.

During a central apnea the lack of input from the respiratory centers causes a reduction in both the tonic and phasic activation of the upper airway muscles, thereby increasing the potential for upper airway obstruction. Airway collapse may thus occur during a central apnea and the airway will be occluded when inspiratory efforts resume. The apnea is then characterized as "mixed" with both central and obstructive components.

In summary, most patients have multiple underlying mechanisms contributing to OSA. Central and obstructive apneas may not be as physiologically distinct as they might at first appear and so most sleep apneas may contain elements of both (see discussion below of "complex" sleep apnea).

Central and complex sleep apnea and Cheyne-Stokes respiration

Teofilo Lee-Chong, Jr (University of Colorado Health Sciences Center, Denver, CO, USA) discussed central sleep apnea (CSA), Cheyne-Stokes respiration (CSR), and complex sleep apnea. Primary CSA is characterized by recurrent cessation of respiration with no associated ventilatory effort during sleep [14]. The exact etiology is unknown but reduction in the $PaCO_2$ level below the apnea threshold may occur in patients with an increased central response to CO_2 or unstable respiratory control mechanisms associated with various CNS disorders. CSA is commonly seen at the onset of sleep and improves during slow-wave and REM sleep. Oxygen therapy may stabilize respiratory control in some patients by reducing hypoxic enhancement of ventilatory response to CO_2, thereby reducing the likelihood of the CO_2 level falling below the apnea threshold.

Additionally, CSA is commonly seen in patients with congestive heart failure (CHF), but should be distinguished from CSR with periodic waxing and waning tidal volume in a crescendo–decrescendo pattern. In both conditions, optimizing therapy for any underlying CHF is warranted [15]. Adaptive servo-ventilation, which increases pressure support during spontaneous periods of hypoventilation and decreases it during periods of hyperventilation, may be useful in CSR [16].

Complex sleep apnea is a term used to describe the development of persistent central apneas on CPAP after obstructive apneas have been abolished [17]. Predisposing factors include baseline hypocapnia, metabolic alkalosis, hypoxia, and possibly an intrinsic heightened ventilatory response to CO_2. Adaptive servo-ventilation has been advocated for treatment of this condition [18].

Sleep in patients with pulmonary disorders.

James Parish (Mayo Clinic, Scottsdale, AZ, USA) presented a lecture on sleep disorders in patients with pulmonary diseases. Patients with chronic obstructive pulmonary disease (COPD) have more arousals and sleep fragmentation with decreased REM sleep compared with healthy persons [19]. Although COPD does not appear to increase the risk of OSA, nocturnal desaturations may be severe during hypopneas and apneas in patients who have both conditions [20]. Patients with COPD are especially likely to have severe desaturations during REM sleep when the thoracic muscles of respiration are inactive and ventilation is dependent primarily on the diaphragm. Other chronic pulmonary diseases are also associated with poor quality sleep.

Asthmatics are at risk of worsening bronchospasm at the usual circadian nadir around 4.00 AM, which may lead to arousals and sleep disruption. Patients with cystic fibrosis have increased sleep fragmentation and those with more severe airway obstruction are at increased risk of severe oxygen desaturations during sleep. Patients with interstitial lung disease have increased arousals, reduced sleep efficiency, less refreshing sleep, more stage 1 sleep, and less REM sleep than healthy persons [21].

Therefore, clinicians should be alert to the possibility of sleep disruption and nocturnal desaturations in patients with chronic respiratory disease. If signs or symptoms are suggestive of nocturnal sleep-disordered breathing, appropriate evaluation should be performed; however, at present routine screening of such patients with sleep studies is not indicated.

Disclosure

Dr Boehlecke has no relevant financial interests in this manuscript.

References

1. Tishler PV, Larkin EK, Schluchter MD et al. Incidence of sleep-disordered breathing in an urban adult population. *JAMA* 2003;**289**:2230–7.
2. Peker Y, Hedner J, Norum J et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med* 2002;**166**:159–65.
3. Mehra R, Benjamin EJ, Shahar E et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2006;**173**:910–6.
4. Ayas NT, Patel SR, Malhotra A et al. Auto-titrating versus standard continuous positive pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. *Sleep* 2004;**27**:249–53.
5. Mulgrew At, Fox N, Ayas NT et al. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study. *Ann Intern Med* 2007;**146**:157–66.
6. White D. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005;**172**:1363–70.
7. Patil S, Schneider H, Schwartz A, Smith P. Adult obstructive sleep apnea. Pathophysiology and diagnosis. *Chest* 2007;**132**:325–37.
8. Okubo M, Suzuki M, Horiuchi A et al. Morphologic analyses of mandible and upper airway soft tissue by MRI of patients with obstructive sleep apnea hypopnea syndrome. *Sleep* 2006;**29**:909–15.
9. Patil S, Schneider H, Marx J et al. Neuromechanical control of upper airway patency during sleep. *J Appl Physiol* 2007;**102**:547–56.
10. Fogel R, Trinder J, White D et al. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. *J Physiol* 2005;**564**:549–62.
11. Malhotra A, Pillar G, Fogel R. et al. Pharyngeal pressure and flow effects on genioglossus activation in normal subjects. *Am J Resp Crit Care Med* 2002;**1675**:71–7.
12. Woodson B, Gasrancis J, Toohill R. Histopathologic changes in snoring and obstructive sleep apnea syndrome. *Laryngoscope* 1991;**101**:1318–22.
13. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med* 2003;**168**:645–58.
14. Eckert D, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest* 2007;**131**:595–607.
15. Olson L, Somers V. Treating central sleep apnea in heart failure: outcomes revisited. *Circulation* 2007;**115**:3140–2.
16. Banno K, Okamura K, Kryger M. Adaptive servo-ventilation in patients with idiopathic Cheyne-Stokes breathing. *J Clin Sleep Med* 2006;**2**:181–6.
17. Morganthaler T, Kagramanov V, Hanak V et al. Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2006;**29**:1203–9.
18. Morganthaler T, Gay P, Gordon N et al. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed and complex sleep apneas syndromes. *Sleep* 2007;**30**:468–75.
19. Weitzenbaum E, Chaouat A. Sleep and chronic obstructive pulmonary disease. *Sleep Med Rev* 2004;**8**:281–94.
20. Sanders M, Newman A, Haggerty C et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med* 2003;**167**:7–14.
21. McNicholas W, Coffey M, Fitzgerald M. Ventilation and gas exchange during sleep in patients with interstitial lung disease. *Thorax* 1986;**41**:777–82.

Reader Survey – Let Us Know What You Think!

Please take a few moments to complete this survey. We would value your opinion.

Please photocopy this page, complete the survey below, and fax it back to Remedica on **(312) 372 0217** from the US or on **+44 (0)20 7759 2951** from the rest of the world. Or you can visit the website and complete the survey online (registration online is FREE):

www.sleepandwakefulness.com

1. We are aiming to provide practical information for sleep specialists, psychiatrists, neurologists, and pulmonologists. How would you rate the information presented in this issue?

	Strongly agree ←				→ Strongly disagree
a) The technical quality of information included in *THE INTERNATIONAL JOURNAL OF SLEEP AND WAKEFULNESS* was acceptable:	1	2	3	4	5
b) The information was relevant to my practice:	1	2	3	4	5
c) The information was presented clearly:	1	2	3	4	5
d) The leading articles provided new information regarding the understanding and treatment of sleep disorders:	1	2	3	4	5
e) The clinical review section was helpful and I would like to see analyses in future issues:	1	2	3	4	5

2. Did you learn anything from the CME activity *THE INTERNATIONAL JOURNAL OF SLEEP AND WAKEFULNESS* that will change the way you practice medicine? ☐ Yes ☐ No

If so, what?.....

3. Is there anything you learned from the CME activity *THE INTERNATIONAL JOURNAL OF SLEEP AND WAKEFULNESS* that prompts you to seek further information that may influence the way you practice medicine in the future? ☐ Yes ☐ No

If so, what?.....

4. Would you like to recommend *THE INTERNATIONAL JOURNAL OF SLEEP AND WAKEFULNESS* to a colleague? ☐ Yes ☐ No

My colleague's email address is: .....

5. What specific topics do you think should be covered in future issues?

.....

Name ..... Job title .....

Institution .....

Address .....

.....

Country ..... Post/zip code .....

Email .....

REMEDICA