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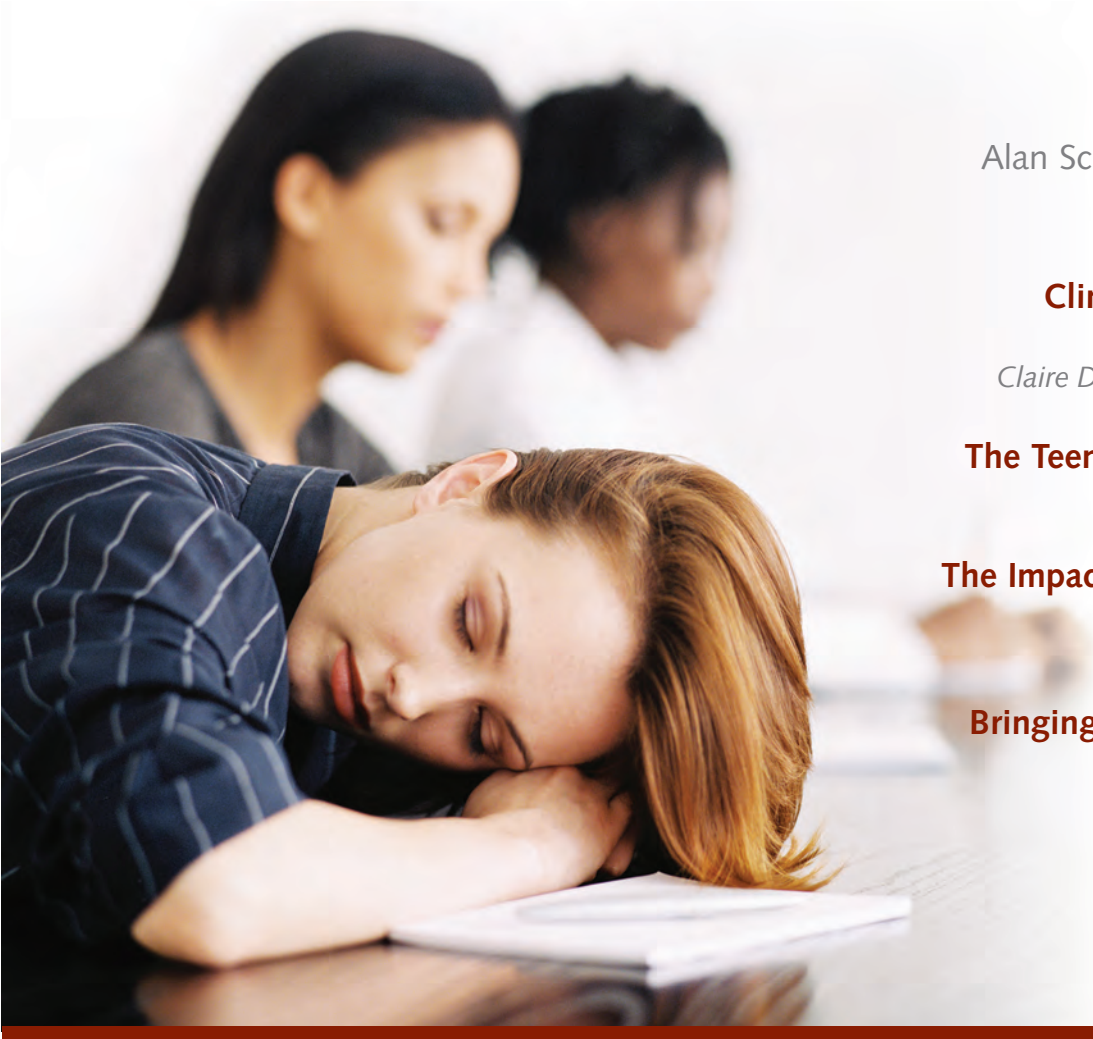

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Aims and Scope

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

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

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

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

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CME

DISCLOSURES

Dr Overeem has received speakers' fees from UCB, European distributor of sodium oxybate. Drs Donjacour, Pelayo, De Vries, and Pedersen have no relevant financial relationships to disclose. Robyn Woidtke is Senior Manager for Clinical Affairs with Ventus Medical Inc.

INTENDED AUDIENCE

This activity is designed to meet the educational needs of sleep specialists, psychiatrists, and other clinicians involved in the management of patients with disorders of sleep and wake.

METHOD OF PARTICIPATION

The information is presented in leading articles, and the readers' knowledge is tested by the CME quizzes. It is anticipated that this activity will take approximately 2 h to complete.

EVALUATION

The evaluation form will provide participants with the opportunity to review the program content and method of delivery, and to identify future educational needs and possible bias in the presentations.

ACCREDITATION

The University of Kentucky College of Medicine designates this educational activity for a maximum of two (2.0) *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity. A passing score of 70% or higher is required for issue of a statement of credit. The University of Kentucky College of Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

INSTRUCTIONS FOR OBTAINING CME CREDIT

Participation in this activity should be completed in approximately 2 h. To successfully complete this program and receive credit, participants must follow these steps:

1. Read the learning objectives.
2. Read the articles' text and tables and review the figures.
3. Complete the registration information on the form included.
4. Read, complete, and submit answers to the self-assessment questions. Participants must respond to all program evaluation questions to receive a certificate by mail.
5. Complete the registration form, post-test answer sheet, and evaluation form at the back of this journal and return to the address provided. This form can also be found as a PDF at www.sleepandwakefulness.com by following the links to CME.

Please note that the website provides the option to print out a PDF of the answers, which requires participants to fax or mail their responses to the University of Kentucky. Alternatively, follow the links to online participation.

Answers should be recorded in the spaces provided overleaf.
One answer is correct for each question.

Clinical and Pathophysiological Aspects of Narcolepsy
Donjacour CE HM and Overeem S.
Int J Sleep Wakefulness 2007;**1**(2)50–60.

1. In the majority of patients, the most debilitating symptom of narcolepsy is:
   A. Cataplexy
   B. Hypnapompic hallucinations
   C. Disturbed nocturnal sleep
   D. Excessive daytime sleepiness
2. What is the most prominent similarity between human and canine narcolepsy?
   A. Recessive mode of inheritance
   B. Cataplexy
   C. Excessive daytime sleepiness
   D. Fragmented night-time sleep
3. Positivity for HLA-DQB1*0602 in patients with a family history for narcolepsy is:
   A. Higher than in sporadic forms of narcolepsy
   B. The same as in sporadic forms
   C. Lower than in sporadic forms
   D. Not associated with DQB1*0602, but with DQA1*0102
4. The most prominent drawback of the currently available stimulants is:
   A. Too low efficacy
   B. Disturbance of nocturnal sleep
   C. Concomittant increase of cataplexy
   D. Side-effects
5. Obesity in narcolepsy is:
   A. Only a minor clinical feature, and caused by increased food intake
   B. Only a minor clinical feature, and caused by decreased locomotor activity
   C. A major clinical feature, of unknown cause
   D. A major clinical feature, and caused by increased food intake
6. HLA-typing:
   A. Is necessary to make a diagnosis of narcolepsy
   B. Is not useful in the diagnosis of narcolepsy
   C. Is useful to diagnose narcolepsy, especially when negative for DQB1*0602
   D. Is useful to diagnose narcolepsy, especially when serological DR2 typing is used
7. Cataplexy:
   A. Is often only partial
   B. Should be witnessed in the hospital before a diagnosis is made
   C. Is typically triggered by fear or sadness
   D. Is only seldom bilateral
8. To make a diagnosis of narcolepsy without cataplexy:
   A. Additional neurophysiological or neurochemical testing is mandatory
   B. CSF hypocretin-1 measurements can be used to objectively confirm a diagnosis of narcolepsy with cataplexy
   C. None of the above statements are true
   D. Both of the above statements are true

The Teenager and Delayed Sleep Phase Syndrome
Pelayo R.
Int J Sleep Wakefulness 2007;**1**(2):61–5.

1. Delayed sleep phase syndrome (DSPS) is a circadian rhythm sleep disorder characterized by:
   A. Chronic sleep-maintenance insomnia and an inability to rise at a time in the morning that is appropriate given the individual's responsibilities
   B. Chronic sleep-onset insomnia and an inability to rise at a time in the morning that is appropriate given the individual's responsibilities
   C. Chronic sleep-onset insomnia and an ability to rise at a time in the morning that is appropriate given the individual's responsibilities
   D. Chronic sleep-maintenance insomnia and an ability to rise at a time in the morning that is appropriate given the individual's responsibilities
2. DSPS prevalence is reported in the *International Classification of Sleep Disorders: Diagnostic and Coding Manual* as:
   A. 1–2%
   B. 7–16%
   C. 32–50%
   D. >50%
3. Once the DSPS patient is able to fall asleep, he or she:
   A. Sleeps soundly and for a normal duration of approximately 8 h
   B. Typically has restless sleep at weekends
   C. Typically experiences parasomnias on school nights
   D. Typically experiences early morning awakenings throughout the week
4. Patients with DSPS often report:
   A. Not having slept at all upon awakening
   B. Never being able to get enough sleep
   C. Feeling refreshed when allowed to awaken spontaneously
   D. Feeling tired but not sleepy upon awakening during summer vacations
5. Which of the following is true of DSPS?
   A. Home schooling for patients should be strongly encouraged
   B. Reasonable accommodations for this condition should be encouraged
   C. Comorbid psychiatric disorders are common
   D. All of the above
6. Which of the following is not true of DSPS?
   A. A canine model of the condition is not available
   B. Patients describe themselves as "night owls"
   C. If allowed to sleep ad lib, patients wake up feeling refreshed
   D. None of the above
7. With regard to the non-pharmacological treatment of DSPS, which of the following is true?
   A. Ease of administration of chronotherapy makes it an ideal treatment
   B. Phototherapy in the evening improves symptoms.
   C. Melatonin on going to bed is more effective than phototherapy in the morning
   D. The patient's motivation to change his or her behavior is essential
   E. All of the above

The Impact of Sleep Apnea on Fatigue: Assessment Issues for Clinical Practice
De Vries J and Pedersen SS.
Int J Sleep Wakefulness 2007;**1**(2):66–9.

1. There are a number of health and safety risks associated with fatigue ensuing from OSAS, including:
   A. Depression
   B. Impaired quality of life
   C. Motor vehicle accidents
   D. All of the above
2. When choosing a self-report instrument with which to assess fatigue in OSAS patients, it is important that this measure:
   A. Assesses sleepiness
   B. Overlaps with depression
   C. Is not confounded by OSAS disease severity and other somatic symptoms
   D. A and C
3. Which of the following statements for the FAS is true?
   A. The FAS is a multi-dimensional scale
   B. Scores on the FAS are biased by gender in patients with sarcoidosis but not OSAS
   C. The FAS consists of 10 items
   D. The FAS is a unidimensional scale consisting of 40 items
4. Items now part of the FAS were originally on the Fatigue Scale along with which other questionnaires(s)?
   A. The Checklist Individual Strength
   B. The Emotional exhaustion subscale of the Maslach Burnout Inventory
   C. The Energy and Fatigue scale of the WHOQOL-100
   D. All of the above
5. The Fatigue Scale was originally developed for use in both hospital and community populations.
   A. True
   B. False
6. Knowledge of the prevalence of fatigue in patients with OSAS is important to:
   A. Determine the proper course of treatment for a patient with OSAS
   B. Identify those patients at risk of adverse secondary outcomes
   C. Measure sleep time in OSAS patients
   D. A and B

Bringing Medical Products to Market in the United States: A Condensed Review for Clinical Investigators
Woidtke R.
Int J Sleep Wakefulness 2007;**1**(2):70–7.

1. The responsibilities of the institutional review board include:
   A. Approval of research and advertising materials
   B. Requesting modifications
   C. Ensuring scientific integrity
   D. A and B
2. The issue of health literacy is an important consideration in:
   A. The clinical research process
   B. The informed consent process
   C. Data collection
   D. The Declaration of Helsinki
3. Phase I in the drug development process:
   A. Tests a product on healthy adult subjects
   B. Is usually performed in a small number of subjects
   C. Determines dosage
   D. Involves all of the above
4. An investigational new drug application includes which of the following sections?
   A. Animal pharmacology and toxicology
   B. Investigator arrangement
   C. Plan for shipping product
   D. Costs to conduct the research
5. In pharmaceutical research, the clinical investigator signs a contract with the sponsor, and thus the US Food and Drug Administration, using which form?
   A. 3500
   B. 1571
   C. 1572
   D. 1000
6. Medical device research requires an investigational device exemption (IDE). The two categories of IDE studies are:
   A. Minimal and significant risk
   B. Non-significant and significant risk
   C. Significant and insignificant risk
   D. Minimal and excessive risk
7. The concept of clinical equipoise aids the investigator in the determination of risk because:
   A. There is certainty that the products under study are equal
   B. The general medical community is not in agreement as to whether one product is better than another
   C. Risk is inherent in all research and it is unrealistic to determine if one product is associated with greater risk than another
   D. Inequality of products is always assumed
8. Informed consent must include:
   A. Autonomy, justice, and beneficence
   B. Risk assessment and conformance to regulatory requirements
   C. Review of participants' literacy level
   D. All of the above
9. Documents which embrace the ethical responsibilities associated with the conduct of clinical research include:
   A. The Belmont Report
   B. The Nuremberg Code
   C. The Declaration of Helsinki
   D. All of the above

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Complete the post-test answer sheet, evaluation form, and registration form and return to:
Attn: Distance Education
UKCPMCE [MEN07157-01]
One Quality Street, 6th Floor
Lexington, KY 40507-1428, USA
Fax: (859) 323-2920

Alternatively the form can be downloaded from *www.sleepandwakefulness.com* by following the links to CME.
Registration is required but is free to physicians and healthcare professionals.

EXAMINATION ANSWERS

Record your answers here by filling in the blank with the correct letter for the corresponding question:

Clinical and Pathophysiological Aspects of Narcolepsy
Donjacour CE HM and Overeem S. *Int J Sleep Wakefulness* 2007;**1**(2):50–60.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____

The Teenager and Delayed Sleep Phase Syndrome.
Pelayo R. *Int J Sleep Wakefulness* 2007;**1**(2):61–5.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____

The Impact of Sleep Apnea on Fatigue: Assessment Issues for Clinical Practice.
De Vries J and Pedersen SS. *Int J Sleep Wakefulness* 2007;**1**(2):66–9.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____

Bringing Medical Products to Market in the United States: A Condensed Review for Clinical Investigators.
Woidtke R. *Int J Sleep Wakefulness* 2007;**1**(1):70–7.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____

Participants will receive a confidential report of their results along with the correct answers to each question.
A certificate of credit will be sent to those who successfully complete the examination.

EVALUATION FORM

	Strongly agree ←			→ Strongly disagree	
1. The activity provided new information I had not yet acquired.	1	2	3	4	5
2. The activity helped increase my knowledge and skills.	1	2	3	4	5
3. The activity content was educational and understandable.	1	2	3	4	5
4. The activity content met its objectives.	1	2	3	4	5
5. The amount of information presented was adequate for my needs.	1	2	3	4	5
6. I felt I absorbed a reasonable amount of the presented materials.	1	2	3	4	5
7. The technical quality of the activity was acceptable.	1	2	3	4	5
8. I would recommend this program to my peers.	1	2	3	4	5
9. Funding for this activity may have come from commercial sponsors. Do you think you were adequately informed of commercial sponsorship or faculty conflict of interest?				Yes	No
10. Do you think the overall activity was biased toward certain commercial products or services?				Yes	No

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Physician License No./State: .....
By signing this certificate, I attest that I have attended the above named continuing medical education program.
Signature: ..... Credit Hours: .....

NEEDS ASSESSMENT

The International Journal of Sleep and Wakefulness, a CME-accredited educational program, systematically identifies, evaluates, and places into clinical context the most important recent studies into the science and medicine of disorders of sleep and wake. It provides rapid access for busy specialists to a critical and clinically relevant review of the developments that will have most impact on their day-to-day practice and is designed to provide management options for clinicians to allow them to better diagnose and treat patients with sleep and wakefulness disorders.
Each issue of *The International Journal of Sleep and Wakefulness* will present carefully constructed leading (review) articles, written by practicing sleep specialists, and intended to equip readers with practical knowledge of the area under discussion. These articles are commissioned to support particular educational themes identified by the Editor-in-Chief, Associate Editor, Editorial team, and readers. This issue of *The International Journal of Sleep and Wakefulness* presents four such leading articles.

LEARNING OBJECTIVES

Clinical and Pathophysiological Aspects of Narcolepsy
Donjacour CE HM and Overeem S
Int J Sleep Wakefulness 2007;**1**(2):50–60.
Goal: To provide an overview of the clinical and pathophysiological aspects of narcolepsy, and to review diagnosis and treatment.
Objectives: After reading this article the reader should be able to discuss:

- The clinical aspects of narcolepsy including excessive daytime sleepiness, cataplexy, and obesity.
- Hypocretin deficiency and genetic factors in the pathophysiology of narcolepsy.
- The diagnosis of narcolepsy with and without cataplexy, and the available treatment options for this disorder and its symptoms.

The Teenager and Delayed Sleep Phase Syndrome
Pelayo R
Int J Sleep Wakefulness 2007;**1**(2):61–5.
Goal: To review the clinical features and management of delayed sleep phase syndrome (DSPS) in the teenaged population.
Objectives: After reading this article, the reader should be able to discuss:

- The background to DSPS and the clinical features of the condition.
- The changes in sleep patterns that occur during maturity, and the reasons why teenagers are particularly prone to DSPS.
- The pharmacological and behavioral approaches to the management of DSPS, and the crucial role of patient motivation in successful treatment of the condition.

The Impact of Sleep Apnea on Fatigue: Assessment Issues for Clinical Practice
De Vries J and Pedersen SS
Int J Sleep Wakefulness 2007;**1**(2):66–9.
Goal: To highlight the prevalence of fatigue in patients with OSAS and to discuss the scales available to measure fatigue.
Objectives: After reading this article, the reader should be able to discuss:

- The impact of OSAS on fatigue.
- The overlap between fatigue and related constructs.
- How fatigue can best be assessed in clinical practice.

Bringing Medical Products to Market in the United States: A Condensed Review for Clinical Investigators
Woidtke R
Int J Sleep Wakefulness 2007;**1**(2):70–7
Goal: To review the regulatory requirements for conducting medical product research in the US, explain the differences between pharmaceutical and medical device research processes, and discuss marketing application options.
Objectives: After reading this article, the reader should be able to:

- Appreciate the differences between drugs and medical devices, and describe the differences in their respective development processes.
- Discuss the different roles and responsibilities of the parties involved in medical product development, namely the US Food and Drug Administration, the investigator, the sponsor, and the institutional review board.
- Describe the ethical responsibilities related to clinical research, with particular emphasis on the issues surrounding the process of obtaining informed consent from study participants.

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CME

Contents

LEADING ARTICLE

Clinical and Pathophysiological Aspects of Narcolepsy

Claire EHM Donjacour, MD[1] and Sebastiaan Overeem, MD[1,2]

[1]Leiden University Medical Center, Leiden; [2]Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Narcolepsy is the prototype of the primary hypersomnias. Excessive daytime sleepiness is the main characteristic of this disorder, with cataplexy and fragmented night-time sleep also among the core symptoms. However, patients also suffer from non-sleep-related problems, such as obesity. Narcolepsy is caused by degeneration of hypothalamic hypocretin (orexin)-producing neurons, although the mechanisms for the cell loss still remain unclear. In recent years, there have been significant additions to both the diagnostic and therapeutic arsenals, an overview of which is provided here. *Int J Sleep Wakefulness* 2007;**1**(2):50–60.

Excessive daytime sleepiness (EDS) is a frequently reported complaint. Most often it is caused by a self-imposed chronic sleep curtailment, or by sleep-related breathing disorders that hamper the quality of night-time sleep enough to cause sleepiness during the day. However, important causes of EDS include the "primary" (central nervous system) hypersomnias. The prototype in this category is narcolepsy, a chronic sleep disorder that has a profound influence on the patient's quality of life. The first symptoms typically occur during adolescence and therefore pose a great burden on the emotional and social development of sufferers. The prevalence of narcolepsy among the general population is almost as high as that of multiple sclerosis, and obtaining a thorough patient history may be sufficient to make a diagnosis. Nevertheless, there often remains a delay of many years between the onset of symptoms and diagnosis. In recent years, the therapeutic arsenal for narcolepsy has been significantly extended and insight into the pathophysiology of this disease has increased tremendously. This concise review will highlight the advances that have been made and provide a broad overview of the current status of the field.

Clinical features

Historically, narcolepsy has always been described as a "tetrad" of symptoms: EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis. However, only a small percentage of patients experience all four symptoms [1,2]. Furthermore, there are several other symptoms that are frequently reported by narcoleptic patients. The most important of which is fragmented night-time sleep. Other symptoms include automatic behavior, obesity, mood disturbances, and memory complaints. It is of paramount importance to cover the whole range of narcolepsy symptoms in the clinical interview (Table 1), especially as these are not always reported spontaneously by patients. EDS is usually the presenting symptom, followed by cataplexy (Fig. 1).

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Excessive daytime sleepiness

EDS is the primary symptom of narcolepsy, and often the most debilitating. It may assume various forms, with a continuous feeling of sleepiness at one end of the spectrum, and sudden involuntary and irresistible "sleep attacks" at the other. Patients often experience a combination of these. Importantly, subjects may not always report EDS as sleepiness, but use descriptions such as being tired, fatigued, having low energy, or feeling lazy. As in healthy individuals, the tendency to fall asleep is much higher during monotonous, non-stimulating activities. Conversely, patients are sometimes able to fight their sleepiness for a period of time by engaging, for example, in physical activity. Daytime sleep episodes are brief, often <20 min, and are typically reported to be refreshing. Although sleep episodes may occur several times a day, the total amount of sleep is not or only slightly increased over a 24-h period due to nocturnal sleep fragmentation [3].

Fragmented night-time sleep

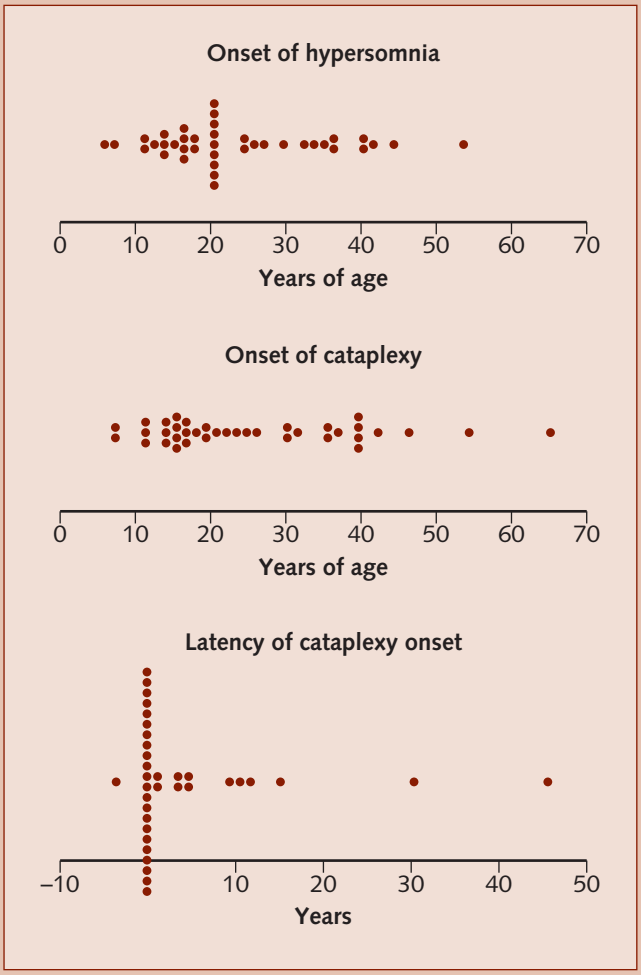
Fragmented nocturnal sleep is a major and common problem in narcolepsy. While patients fall asleep very fast,

Table 1. Topics to cover in a clinical interview for narcolepsy.

General	Age at onset and presenting symptom
EDS	Onset and frequency of involuntary sleep episodes Number of planned naps Duration of naps (both involuntary and planned) Are naps refreshing, and do they worsen or improve sleepiness?
Nocturnal	Time in/out of bed, subjective sleep latency, number and duration of sleep awakenings, does the patient remain in bed when awake? Does the patient feel refreshed in the morning? Sleep hygiene, and symptoms of other sleep disorders (e.g. apnea, periodic limb movement disorder, REM sleep behavior disorder)
Cataplexy	Description of a typical attack, either partial or complete Attack duration, frequency, and triggers Does the patient have preserved consciousness during the attack? Has patient suffered an injury during an attack?
Hypnagogic hallucinations	Duration, frequency Description of a typical example, stereotyped contents, fear/anxiety
Sleep paralysis	Duration, frequency, possible co-occurrence with hypnagogic hallucinations
Automatic behavior	Description of automatic behaviour and frequency
Memory	Complaints, type of disturbances, onset
Mood	Mood disturbances, onset, severity
Weight change	Any change at time of onset of narcolepsy symptoms, obesity
Eating habits	Appetite, (binge) eating, eating at night, craving for sweets
Sexual history	Sexual problems, onset Possible relation with medication
Family history	Relatives with narcolepsy or other sleep disorders
Social history	Profession, relation Impact of disorder on these areas
Habits	Coffee, tea, energy drinks, alcohol, and their influence on EDS

EDS: excessive daytime sleepiness; REM: rapid eye movement.

Figure 1. Schematic illustration of the age at onset of EDS and cataplexy and the interval in years between the onset of EDS and cataplexy in patients with narcolepsy and definite cataplexy.



EDS: excessive daytime sleepiness. Figure redrawn with permission from [91].

numerous awakenings may follow. These awakenings are usually short but can sometimes last for hours, forcing patients to get out of bed. On polysomnography recordings, nocturnal sleep fragmentation is characterized by frequent arousals and an increased number of shifts between sleep states. Importantly, fragmented night-time sleep is not the cause of EDS; while improving nocturnal sleep may sometimes alleviate daytime sleepiness, EDS will never disappear [5]. In addition, other sleep-related disorders such as periodic limb movement disorder, sleep apnea, and rapid eye movement (REM) sleep behavior disorder may contribute to the disturbed nocturnal sleep in narcolepsy patients [4]. However, with the possible exception of sleep apnea (which may also pose diagnostic difficulties), these sleep disturbances are often of unclear significance.

Cataplexy

The most specific symptom of narcolepsy is cataplexy, derived from the Greek word καταπλησσω meaning

"to strike down". Cataplexy is defined as a sudden bilateral loss of muscle tone with preserved consciousness, and triggered by emotions. The combination of cataplexy and EDS is pathognomonic for narcolepsy.

Cataplexy can be triggered by a diversity of emotions. The most often reported triggers are laughter, hearing a joke, or feeling excited [6,7]. Other examples include an unexpected meeting with an acquaintance or the feeling of elation when anticipating the perfect smash in a game of tennis. Patients need to be in a relaxed state to easily suffer a cataplectic attack and, consequently, attacks cannot generally be provoked during medical consultation. When a physician tries to tell a joke, the patient will not experience cataplexy; however, after the consultation when telling a friend in the waiting room about this "crazy" doctor, cataplexy is likely to occur.

Most cataplectic attacks are partial, resulting for example in sagging of the jaw with blurred speech or buckling of the knees. Partial attacks may evolve into a complete loss of skeletal muscle tone leading to a fall but, because of its gradual onset, patients can usually support themselves preventing injury. Cataplexy attacks last only for a short time, from several seconds to a few minutes. A longer duration is most likely to be the result of consecutive attacks, for example in a situation where the patient hears friends continuing to joke – consciousness is preserved, so patients are fully aware of their surroundings. In contrast to the onset, cataplectic attacks typically end abruptly. An attack will occasionally blend into REM sleep.

Hypnagogic hallucinations

Hypnagogic hallucinations are vivid dreamlike experiences that occur upon falling asleep. The auditory, visual, or tactile sensations are usually felt to be real, and are often bizarre and frightening. The perception of intruders, with people or animals standing over or lying under the bed is particularly common [8]. Similar episodes may present when waking, and are called hypnopompic hallucinations. Hypnagogic hallucinations also occur in the general population. Since hypnopompic hallucinations are less common, they may be a better indicator of narcolepsy [9].

Sleep paralysis

Sleep paralysis is the inability to move at sleep onset or, more commonly, when awakening. While the patient is awake, it is impossible for them to move their arms or legs or even open their eyes, and it can be extremely distressing, especially when occurring for the first time. Hypnagogic or hypnopompic hallucinations often occur during sleep paralysis. Stress, sleep deprivation, or uncomfortable sleep position may have a promoting effect on sleep paralysis. While the prevalence of sleep paralysis in narcolepsy is high (about 50%), just over 5% of the general population will experience sleep paralysis at least once in their lifetime [10].

Obesity

It has long been known that narcoleptics tend to be overweight, but this was usually attributed to inactivity due to EDS and received little attention. However, new epidemiological studies have clearly shown that obesity is a major symptom of narcolepsy [11,12]. Obesity (body mass index [BMI] ≥30 kg/m^2) occurs more than twice as often in patients with narcolepsy than among the general population. In nearly 40% of narcolepsy patients, the waist circumference reaches a level that warrants medical intervention to prevent possible long-term complications from excessive body fat (Fig. 2). The cause of weight gain in narcolepsy is unknown. Some patients complain about a tendency to binge eat, especially during waking periods at night. However, in a study using cross-checked dietary histories, it was shown that over a period of 24 h individuals with narcolepsy tended to consume fewer calories than controls, particularly carbohydrates [13]. Patients with idiopathic hypersomnia where shown to have a lower BMI than narcoleptics, indicating that inactivity due to EDS is not likely to account for the obesity [11]. Thus, it seems possible that mechanisms such as a lowered metabolic rate underlie the increase in body weight seen in subjects with narcolepsy.

Other symptoms

Automatic behavior is frequently reported by patients, and is characterized by semi-purposeful and often inappropriate activity during a state of drowsiness. Episodes typically involve the continuation of activities that do not require extensive skill [14]. Patients may start writing nonsensically and keep on writing while drifting off the lines, or throw away their money instead of the receipt after getting money from a bank machine.

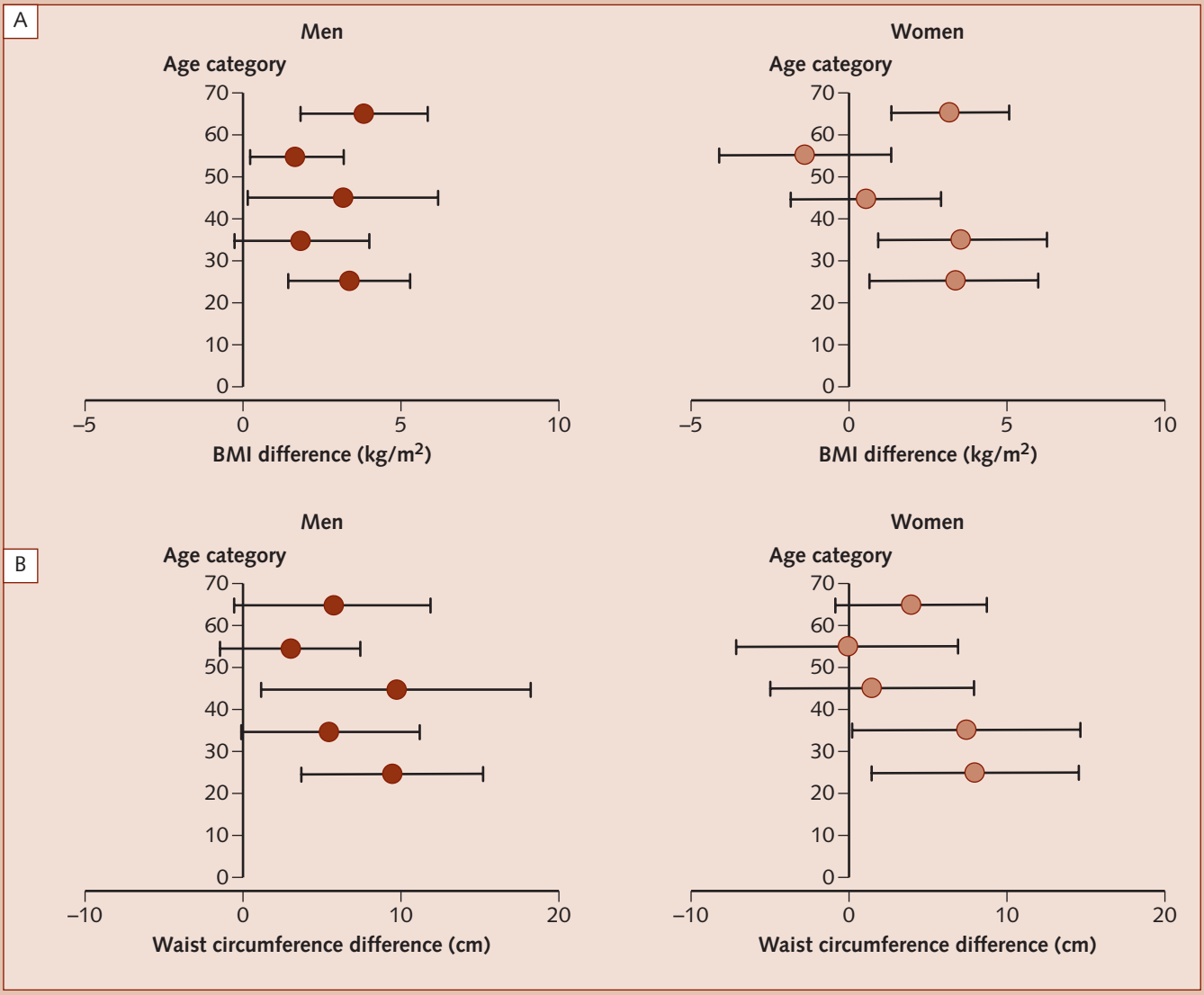
Many narcolepsy patients have memory complaints. Interestingly, when formally tested, they do not always show objective memory deficits [15,16]. The reason for this is unclear; patients may, for example, be more vigilant in a testing situation than in everyday life.

Up to 30% of narcoleptics fulfill the criteria for depression, and the prevalence of depressive symptoms is even higher [17]. Sexual dysfunction is also common (decreased libido, impotence). This is due, in part, to the side effects of drugs commonly used to treat narcolepsy, such as tricyclic antidepressants for cataplexy.

Epidemiological aspects

In Western countries, narcolepsy has an estimated prevalence of 20–60 per 100 000 inhabitants. There may be

Figure 2. Differences in BMI (**A**) and waist circumference (**B**) in narcolepsy patients versus controls, for men (left) and women (right). Data are given per age category (mean difference with 95% confidence interval).



BMI: body mass index. Figure redrawn with permission from [11].

regional differences, with the highest reported prevalence in Japan and the lowest in Israel, although these disparities are likely to result from variable diagnostic criteria or study designs. Little information is available on the incidence of narcolepsy; incidence numbers are estimated around 0.74 per 100 000 person–years [18].

Men and women are affected equally. Onset occurs at age 15–30 years in the majority of patients, with a mean age of 24 years [18]. One study found a bimodal distribution in the age at onset with a first peak occurring at adolescence (mean 14.7 years) and a second at the age of 35 years (Fig. 3) [19]. Approximately 6% of narcoleptics have symptoms before the age of 10 years. Symptoms typically occur gradually, with EDS as the presenting symptom and cataplexy developing in the following few years. Only a minority of patients develop the "full-blown" picture of narcolepsy and around 10–15% display the classical tetrad [1,2]. Once symptoms have developed, there are usually only minor fluctuations in severity, although there may be some decrease in cataplexy severity later in life.

The burden of narcolepsy

Narcolepsy has a striking negative effect on quality of life and affects virtually all life domains [20–22]. Questionnaire studies show that the impact of narcolepsy is more severe than with other chronic conditions such as epilepsy. Patients not only report a great impact on job performance and schooling, but also on relationships, social life, and leisure

Figure 3. Density curves of age at onset in two cohorts of patients with narcolepsy from (**A**) Montpellier, France and (**B**) Montreal, QC, Canada.

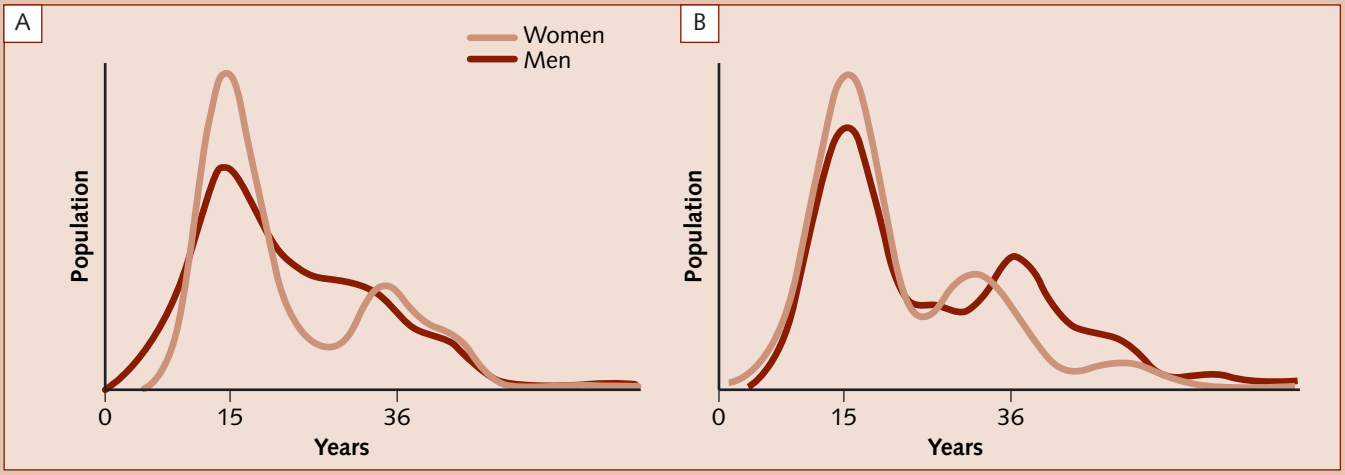


Figure redrawn with permission from [19].

activities. Driving is prohibited in many countries. Onset of EDS typically occurs during the adolescent years, and psychosocial and academic problems are almost universal. Daniels et al. reported that >50% of narcolepsy patients had difficulty concentrating in class and felt that they had achieved less than they were capable [23]. These aspects further underscore the necessity of prompt diagnosis and appropriate treatment.

Pathophysiology

In the last decade, knowledge of the pathophysiology of narcolepsy has increased significantly. From a sleep disorder of unknown cause [24], through psychoanalytical theories [25], it is now known that narcolepsy is a neurodegenerative disorder with the hypothalamus being the critical affected brain area [26].

Genetic aspects

In its typical form, human narcolepsy is a sporadic disease [27]. However, first degree relatives still have a 10–40-fold increased risk of developing narcolepsy compared with the general population [28]. True familial narcolepsy is rare; only 1–2% of all narcoleptics are part of a family with multiple affected generations [28]. In the early 1980s, the first reports emerged on the association of sporadic narcolepsy and specific human leukocyte antigen (HLA) subtypes. Over 90% of sporadic narcolepsy patients are positive for HLA-DQB1*0602, compared with approximately 25% of the general population [29]. As there are several autoimmune disorders closely associated with specific HLA types, these findings implied an autoimmune genesis for narcolepsy (see below). In addition, there may be other genetic factors involved in the pathophysiology of the disease. Thus far, reports have shown associations with the genes for tumor necrosis factor-α and catechol-*O*-methyltransferase [30,31]. The few available genome-wide screenings yielded linkage to two (large) genomic regions on chromosome 4p13-q21 [32] and 21q [33,34], but no candidate genes have as yet been identified.

Hypocretin (orexin) defects in animal narcolepsy

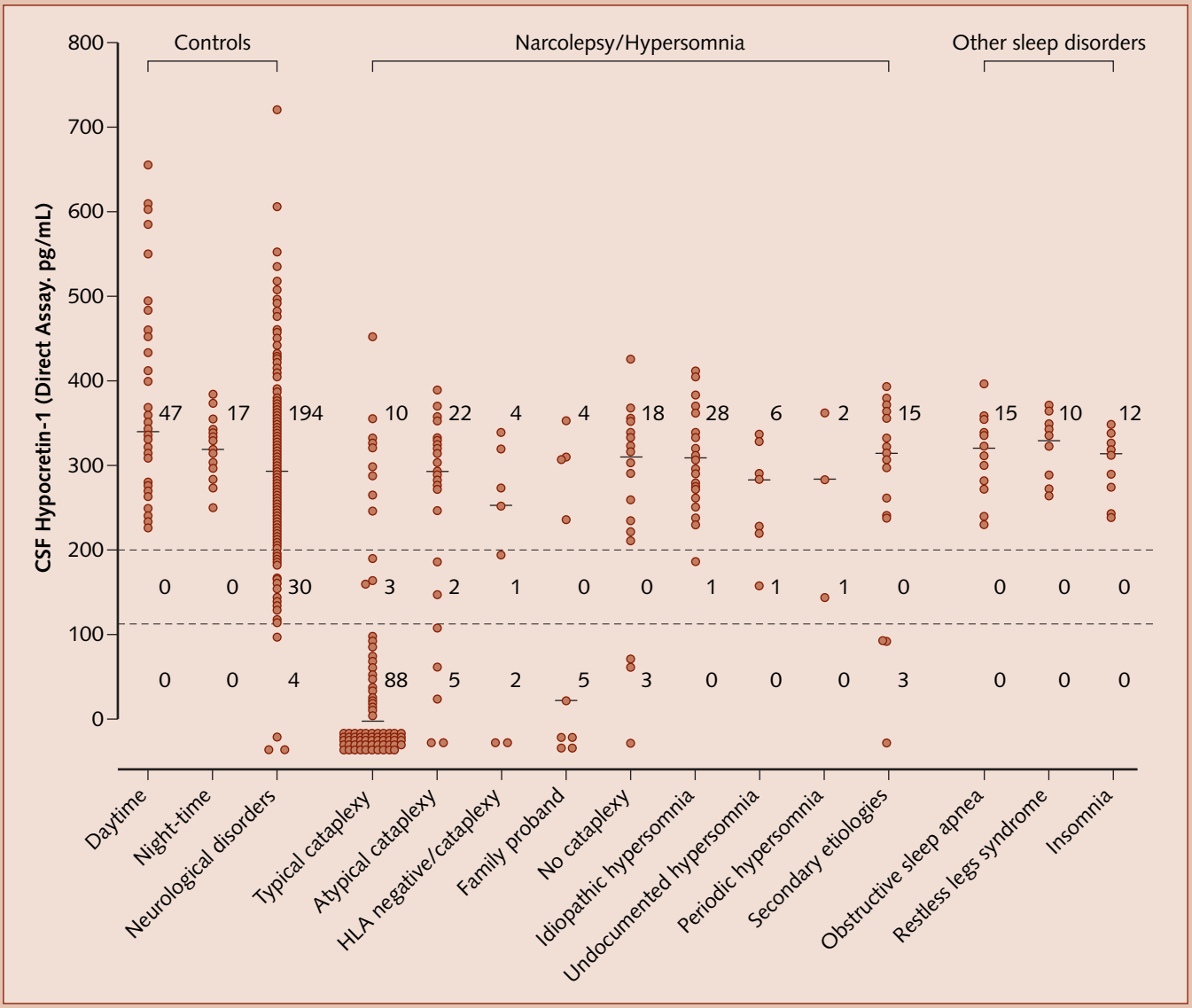
Canine narcolepsy is strikingly similar to the human condition, and cataplexy is the most prominent feature [35]. In narcoleptic Doberman Pinschers and Labrador Retrievers, the phenotype is transmitted as an autosomal recessive trait with full penetrance [36]. A 10-year project to clone the responsible gene was started at the end of the 1980s. In 1999, this gene was identified to be *Hcrtr-2*, coding for one of the two known receptors for the hypothalamic neuropeptide hypocretin (also known as orexin) [37].

Only 2 weeks after the publication of the canine narcolepsy gene, Yanagisiwa and colleagues, who co-discovered the hypocretins a year earlier [38,39], reported on the phenotype of *preprohypocretin* knockout mice [40], and convincingly showed that these animals had both "clinical" and polysomnographic features of narcolepsy.

Hypocretin (orexin) defects in human narcolepsy

Shortly after the implication of the hypocretin system in the pathogenesis of narcolepsy in animals, the link with the human disorder was established. In a first study, hypocretin-1 was measured in the cerebrospinal fluid (CSF) of nine narcoleptic patients and eight control subjects. In seven patients, but in none of the controls, there was no detectable CSF hypocretin-1 [41]. These findings were quickly followed

Figure 4. CSF hypocretin-1 levels in various categories of sleep disorders. Each dot represents a single patient. Hypocretin-1 levels ≤110 pg/mL were determined to be diagnostic for narcolepsy. Concentrations >200 pg/mL best describe healthy controls. Levels below the detection limit of the assay are shown as 0. The number of subjects with values in each category is shown. Note that undetectable hypocretin levels are virtually specific for narcolepsy, especially narcolepsy with typical cataplexy. The only non-narcolepsy patients with undetectable levels are three patients with a severe form of Guillain-Barré syndrome.



CSF: cerebral spinal fluid; HLA: human leukocyte antigen. Figure redrawn with permission from [44].

by larger studies, and it is now clear that >90% of patients with sporadic, HLA DQB1*0602-positive narcolepsy, are hypocretin deficient [42–44]. Furthermore, hypocretin-1 deficiency is highly specific for narcolepsy: levels were normal in a large group of patients with various other sleep disorders (Fig. 4) [44]. Using both *in situ* hybridization in frozen brain tissue and immunohistochemistry analysis fixed human brains, it was shown that there is no detectable hypocretin mRNA or peptide in the hypothalamus of narcoleptic subjects [26,45]. In addition, one study found a significantly increased number of reactive astrocytes in the hypothalamus, suggesting neuronal degeneration [45]. As two co-localizing markers in hypocretin neurons, dynorphin and neuronal activity-regulated pentraxin, were also shown to be absent in narcoleptic brains, it is likely that human narcolepsy results from a selective degeneration of hypocretin-producing neurons [46,47]. Unfortunately, imaging studies have yielded conflicting results and, as yet, there is no *in vivo* evidence for structural damage in the hypothalamic area [48–52].

The cause of the hypocretin deficiency

Although there may be a degenerative process affecting hypocretin cells, the cause of such a process remains unknown. Mainly based on the strong HLA association, the prevailing hypothesis suggests that an autoimmune reaction may be responsible. Thus far, the majority of studies have focused on markers of humoral autoimmunity, especially the possible presence of circulating antibodies against (part of) the hypocretin system. Taken together, the results have largely been negative [53–55], although one study found an increased CSF immunoglobulin G (IgG) fraction reacting with rat hypothalamic extract [56]. In another study, Smith et al. purified the IgG fraction from peripheral blood in nine patients and nine controls, and injected these into mice [57]. After the mice were sacrificed, the investigators tested the response of the detrusor muscle to the muscarinic agonist carbachol *in vitro*. The reaction was increased in those mice that had received the IgG fraction from narcolepsy patients. Since the underlying mechanism leading to narcolepsy is unclear, these results warrant replication.

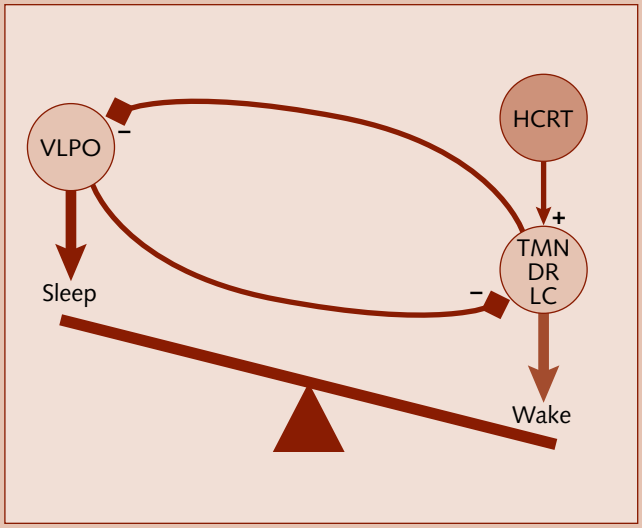
In a number of recent open-label studies, narcoleptics were treated with intravenous immunoglobulins (iv Ig), in some cases resulting in a reduction in the severity and frequency of cataplexy [58–60]. These results call for a double-blind trial into the therapeutic use of ivIg; however, as the effects of iv Ig are highly complex, they are not proof for an underlying autoimmune process in narcolepsy [53,61].

From hypocretin defect to clinical symptoms

Narcolepsy models are currently being developed to link the hypocretin deficiency with the clinical symptoms. For EDS, the sleep switch model of Saper et al. provides an excellent explanation [62]. In this model, mutual inhibitory connections between the active sleep and wake regions of the brain result in a "flip-flop"; an inherently unstable switch that is sensitive to even slight disturbances (Fig. 5). To function properly, it is necessary to stabilize the switch. The excitatory projections of hypocretin neurons to several wake-promoting systems keep the switch in the wake position [62,63]. Loss of hypocretin transmission results in an unstable sleep switch, with frequent changes between wakefulness and sleep, and *vice versa*.

For cataplexy, the theoretical framework is less clear. Based on the fact that strong emotions such as laughter can induce sub-clinical signs of motor inhibition even in healthy subjects [64], it may be necessary to have a brain system that suppresses this tendency towards paralysis and essentially prevents cataplexy from occurring [65]. Recent studies measuring the activity of hypocretin neurons in freely moving rats may support this view [66,67]. The hypocretin neurons were relatively silent during the majority of the day and were most activated when the animals were confronted with "emotional" stimuli, such as types of food not encountered previously, or a new environment. It was hypothesized that the hypocretin system is necessary to prevent the onset of motor inhibition during situations of this kind [66].

Figure 5. Schematic illustration of a proposed "flip-flop" mechanism controlling sleep. The distinct sleep and wake promoting areas in the brain have reciprocal inhibition connections, resulting in a "bi-stable switch" that avoids intermediate states. However, small pertubations tend to shift the switch from one state to the other very rapidly; therefore, a stabilizing factor is needed. The hypocretin system stabilizes the switch in the wake position through excitatory input on the wake-side of the switch.



DR: dorsal raphe; HCRT: hypocretin; LC: locus ceruleus; TMN: tuberomamillary nucleus; VLPO: ventrolateral preoptic area. Figure redrawn with permission from [62].

Diagnosis

In 2005, the International Classification of Sleep Disorders (ICSD) was revised [68]. The new ICSD narcolepsy criteria now contain an explicit distinction between narcolepsy with and without cataplexy, while symptoms such as sleep paralysis and hypnagogic hallucinations are no longer listed as diagnostic features. Furthermore, measurement of CSF hypocretin-1 levels has been added as an objective diagnostic tool. The diagnostic criteria are listed in Table 2.

Narcolepsy with cataplexy

Essentially, when there is EDS and clear-cut cataplexy, a diagnosis of narcolepsy with cataplexy can be made based on the patient's history alone. However, determination of cataplexy can be difficult, especially when there are only partial attacks. Due to the consequences of narcolepsy, both

Table 2. The International Classification of Sleep Disorders criteria for narcolepsy.

Essential diagnostic criteria of narcolepsy with cataplexy:

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for ≥3 months.

B. A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present.

C. The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT. The mean sleep latency on MSLT is ≤8 min and ≥2 sleep-onset REM periods are observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test. Alternatively, hypocretin-1 levels in the cerebrospinal fluid are ≤110 pg/mL, or one-third of mean normal control values.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

The diagnostic criteria of narcolepsy without cataplexy include criteria A and D, whilst criteria B and C are as follows:

B. Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported.

C. The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed by an MSLT. In narcolepsy without cataplexy, the mean sleep latency on MSLT is ≤8 min and ≥2 sleep-onset REM periods are observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test.

MSLT: multiple sleep latency test; REM: rapid eye movement.

socially and therapeutically, it is recommended that the diagnosis is objectively confirmed. The mainstay in this respect remains the Multiple Sleep Latency Test (MSLT) [69,70]. A mean sleep latency of <8 min, together with two sleep-onset REM periods, is considered diagnostic. The MSLT should be preceded by a nocturnal polysomnography assessment showing ≥6 h of sleep, and which is also used to detect other nocturnal sleep disorders, such as sleep-disordered breathing. Alternatively, CSF hypocretin-1 levels can be measured, with low or undetectable levels confirming the diagnosis [44].

Narcolepsy without cataplexy

When there is no history of cataplexy, it is more difficult to establish a diagnosis of narcolepsy. Firstly, one needs to exclude other causes of EDS. Aside from nocturnal sleep disorders such as sleep-disordered breathing, chronic sleep curtailment is frequently a cause, especially in young people. Furthermore, the abovementioned MSLT or hypocretin-1 criteria are mandatory to make the diagnosis (Table 2). Nevertheless, it often remains difficult to differentiate narcolepsy without cataplexy from, for example, idiopathic hypersomnia. In fact, it has been debated whether narcolepsy without cataplexy is actually part of a "true continuum" with narcolepsy with cataplexy, sharing a common pathophysiology [71].

Additional diagnostic tools

Questionnaires can be used to measure subjective sleepiness and the Epworth Sleepiness Scale is most often used for this purpose [72]. Although not diagnostic, these scales give the physician an idea of the severity of perceived sleepiness, and may sometimes be useful to monitor treatment effect.

A recent study showed that a behavioral measure of vigilance, the Sustained Attention to Response Task (SART), often shows as many abnormalities as the MSLT in narcoleptics [73]. Future studies are required to study the specificity of the test; however, the idea of a laboratory test to measure part of a patient's functional status seems very appealing.

Although >90% of patients with typical sporadic narcolepsy with cataplexy are positive for the HLA subtype DQB1*0602, over 25% of the normal population are carriers. More importantly, in clinically difficult cases (no cataplexy, very young onset, positive family history) HLA positivity is much lower. HLA typing is therefore not useful in the routine diagnostic workup for narcolepsy [71]; however, for research purposes, HLA typing remains a very important tool to define homogenous and clear-cut patient groups.

Treatment

Every narcoleptic patient should be advised to live a normal life, going to bed and getting up at a similar time every day. Scheduled naps can alleviate sleepiness for a while, and may be advised [74]. Likewise, a short nap before demanding activities may be helpful. However, in the majority of patients, pharmacological treatment is necessary [8,75].

While, for practical purposes, treatment is considered separately for EDS, fragmented night-time sleep, and cataplexy, this distinction is somewhat artificial. Many patients report the threshold for cataplexy to be lower when they are sleepy; therefore, stimulant treatment can sometimes also help to fight cataplexy. In practice, it is advised to start treating the most disabling symptom first, and to tailor drug schedules and dosages individually. Combination therapy is often necessary [75].

It must be emphasized that drug therapy is purely symptomatic. While cataplectic attacks can often be completely abolished, EDS will never completely disappear with treatment.

Treatment of EDS

Stimulants remain the mainstay of treatment for EDS (Table 3) [79,80]. They include the typical CNS-stimulatory

Table 3. Examples of drugs commonly used in the treatment of narcolepsy.

	Daily dose	Usual number of doses/day
Treatment of EDS		
Dextroamphetamine	5–60 mg	1–2
Methamphetamine	10–50 mg	1
Methylphenidate	10–60 mg	2–3
Modafinil	200–400 mg	1
Treatment of cataplexy, sleep paralysis, and hypnagogic hallucinations		
Tricyclics		
Clomipramine	10–150 mg	1–3
Imipramine	10–150 mg	1–3
SSRIs		
Fluoxetine	20–60 mg	1
Fluvoxamine	100–300 mg	1–2
SNRIs		
Venlafaxine	37.5–150 mg	1–2
Sodium oxybate	3–9 g	2 nocturnal doses

SNRI: serotonin–norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors.

amphetamine-derivates and the non-amphetamine-like substance, modafinil.

Amphetamines used in the treatment of narcolepsy include dextroamphetamine, methamphetamine, and methylphenidate. The mode of action of these drugs is complex, but the central mechanism entails the enhancement of the release of catecholamines (dopamine and noradrenaline) as well as uptake inhibition. In higher doses, other mechanisms start to play a role, including interaction with monoamine transporters and inhibition of monoamine oxidase. Side-effects are often related to alpha-adrenergic stimulation, including tachycardia and an increase in systolic and diastolic blood pressure. Other side effects include restlessness, vasomotor disturbances, and occasionally mild gastrointestinal disturbances [79,80]. Irritability, agitation, and headache may occur with longer term use. Induction of psychiatric symptoms, such as psychosis, is rare. Amphetamines taken late in the afternoon or in the evening may further disturb nocturnal sleep. Tolerance to amphetamine-derivate drugs occurs in many patients, necessitating higher doses [79,80]. Interestingly, addiction almost never occurs in narcolepsy patients [75]. Recent studies suggest that the hypocretin system mediates reward function in the brain, and may explain why hypocretin-deficient narcoleptic patients seem less likely to develop addiction [76–78].

The wake-promoting agent modafinil is a primary metabolite of adrafinil, a vigilance-promoting compound discovered in France in the 1970s [75,79,80]. Its mechanism of action is still a matter of debate – initially, an alpha-adrenergic action was suggested but later studies have questioned this and recent evidence suggests that an increase in dopamine signaling is an important mediator [81]. However, in contrast to the amphetamines, modafinil does not seem to increase the release of dopamine and does not inhibit monoamine oxidase. Furthermore, modafinil does not induce the typical behavioral effects of amphetamines in rodents such as compulsive licking, grooming, and sniffing.

In clinical practice, the main advantage of modafinil is the low incidence and severity of side-effects [82]. Headaches and nausea are among the most frequent side-effects, but tend to disappear over time; irritability and agitation occur much less often. Hypertension and tachycardia may be seen when very high doses are used. Modafinil may also lower plasma estrogen levels.

Modafinil has a relatively long duration of effect, and is dosed once a day [82]. The most commonly used amphetamine, methylphenidate, is much shorter-acting, and has to be taken 3–4 times a day. A long-acting form of methylphenidate is available, but experience of this drug with narcolepsy patients is still limited. However, methylphenidate can be used "on-demand", especially in mild cases, for example before a meeting or a theater visit [75]. It may sometimes be useful to combine modafinil with on-demand methylphenidate, although this is not recommended as a first-line choice. Recent studies using sodium oxybate in relatively high doses (up to 9 g/night) suggest that the compound may reduce sleepiness, resulting in a dose-sparing effect on stimulants [83–85].

Treatment of cataplexy, hypnagogic hallucinations, and sleep paralysis

In general, the amelioration of cataplexy is associated with a reduction of hypnagogic hallucinations and sleep paralysis. Tricyclic antidepressants are among the most effective agents, sometimes in surprisingly low doses [75]. Those most commonly used include imipramine, protryptiline, and clomipramine. Side effects, and to a lesser extent, tolerance, are a major drawback. Side effects are largely due to the anticholinergic properties of these drugs; the most frequently reported are dry mouth, increased sweating, sexual dysfunction (impotence, delayed orgasm, erection, and ejaculation dysfunction), weight gain, tachycardia, constipation, blurred vision, and urinary retention. Many

alternatives have been proposed to the tricyclics, including selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or fluvoxamine. In contrast to the tricyclics, SSRIs usually require a relatively high-dose, which can sometimes negate their more favorable side-effect profile. On theoretical grounds venlafaxine, a noradrenalin/serotonin reuptake inhibitor, has gained popularity as a first-choice drug, although no studies on its efficacy have been published. Acute withdrawal from antidepressants may severely aggravate cataplexy, sometimes leading to a status cataplecticus (cataplexy that occurs repeatedly for hours or days).

In 2002, the sedative–hypnotic sodium oxybate (gammahydroxybutyrate; GHB) was approved by the US Food and Drug Administration for the treatment of cataplexy. GHB occurs naturally in the brain, but its mechanism of action in narcolepsy is not precisely known. Its effects are thought to be mediated through both γ-aminobutyric acid$_B$ (GABA$_B$) and specific GHB receptors. The earlier open-label and small, controlled studies showing the efficacy of sodium oxybate in the treatment of cataplexy [86–90] have now been confirmed in a number of large trials [91–93]. Because of its short half-life, sodium oxybate is administered in two divided nocturnal doses, the first at bedtime and the second at 3–4 h later. It acts rapidly, and should be taken when the patient is already in bed and after the second dose for the night has been prepared. In contrast to benzodiazepines, sodium oxybate increase the amount of slow-wave sleep, and tolerance is rare. With low doses, there are few side effects and these are generally mild. Higher doses, up to 9 g/night, are more effective, although the number of side effects may increase. Dizziness and nausea are most frequently reported, but urinary incontinence and somnambulism are the most troublesome. When the latter occur, reducing the dose is usually sufficient. The ingestion of very high doses may lead to coma and respiratory depression. Airway maintenance is of utmost important in these cases, as intoxications may induce vomiting and consequently aspiration. Unfortunately, the drug has been popularized as a substance of abuse over the last years, and therefore its use must be closely monitored.

Treatment of disturbed nocturnal sleep

Although disturbed nocturnal sleep can be a major complaint among narcolepsy patients, effective treatment options are unfortunately limited. Short-term effects of benzodiazepines have been described [75], and sodium oxybate seems to be the drug of choice for fragmented night-time sleep due to its efficacy and low probability of tolerance.

Conclusions and future perspectives

Recent advances in understanding the pathophysiology of narcolepsy have increased awareness of this disorder. Not only does this have scientific value, but it also benefits the patient. The improved knowledge is likely to heighten the diagnostic vigilance of physicians and, together with the increased number of treatment options, this will result in an improved quality of life for individuals with narcolepsy. Based on the new pathophysiological insights, it is expected that in the following years, new – perhaps even causal – treatments will be developed.

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The Teenager and Delayed Sleep Phase Syndrome

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LEADING ARTICLE

Delayed sleep phase syndrome (DSPS) is a common circadian rhythm sleep disorder in teenagers that is characterized by chronic sleep-onset insomnia and an inability to arise in the morning at a time appropriate to an individual's social and academic responsibilities. The syndrome can result in frequent school tardiness and absenteeism, and the symptoms may mimic those of depression. DSPS is not difficult to diagnose once clinical suspicion has been aroused, but obtaining a satisfactory response to treatment is more challenging. Behavioral and pharmacological treatments, either separately or in combination, have been utilized in the treatment of the condition; however, attempts to correct the sleep schedule meet with little success if the individual is not persuaded to alter the lifestyle factors that influence his or her late bedtime, particularly at weekends. Therefore, the importance of patient motivation in the treatment of this disorder cannot be overemphasized. This article will review the clinical features and management of DSPS in teenagers. *Int J Sleep Wakefulness* 2007;**1**(2):61–5.

Within the spectrum of clinical sleep disorders, delayed sleep phase syndrome (DSPS) is one of the easiest diagnoses to make. However, it is one of the most frustrating conditions to remedy, particularly because treatment requires the desire or motivation of the patient to change his or her behavior to meet societal demands, such as those of school or work.

DSPS prevalence is reported in the *International Classification of Sleep Disorders: Diagnostic and Coding Manual* as 7–16%, with the condition typically developing in adolescence [1]. Unless a teenager presenting at a sleep clinic has obstructive sleep apnea, his or her sleep disorder diagnosis will, almost inevitably, be DSPS.

DSPS is a circadian rhythm sleep disorder characterized by chronic sleep-onset insomnia and an inability to rise at a time in the morning that is appropriate, given the individual's commitments. Once the DSPS patient is able to fall asleep, he or she sleeps soundly and for a normal duration of approximately 8 h [1]. When not required to maintain a strict sleep schedule (for example, at weekends, or during vacations and holiday periods) patients will awaken spontaneously, albeit late in the morning or early in the afternoon.

A historically important article coauthored by several prominent sleep experts originally described the syndrome in 1981 [2]. Weitzman et al. reported on a group of patients, younger than the general insomniac population, who did not have a specific psychiatric disorder. These patients did not have the classic early morning awakening characteristic of insomnia, and in fact followed the opposite pattern, having sleep-onset insomnia. Most importantly, they woke feeling refreshed when allowed to set their own schedules. The authors proposed this to be "a disorder of the circadian sleep–wake rhythm in which the 'advance' portion of the [light] phase response curve is small" [2]. The phase response curve illustrates the relationship between the timing of administration of a drug or treatment and the corresponding circadian phase shift, and presumably also the timing of sleep.

DSPS can be conceptualized as resulting from a clock for which the time can only be readily adjusted in one direction, as it is intrinsically easier for patients to fall asleep later than usual, rather than earlier. People susceptible to DSPS may have more difficulty adjusting to an earlier sleep time than others [3–5].

Clinical features of DSPS

After the initial description of DSPS, the clinical features of the syndrome were described in a case series of 22 adolescents by Thorpy et al. in 1988 [6]. Habitual "weekday" and "weekend" sleep patterns were simulated in a protocol of polysomnographic readings, in which nine individuals participated. During the weekend sleep period, the investigators noted a significant increase in rapid eye movement (REM) sleep and total sleep time. Between the

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two sleep periods a multiple sleep latency test was performed to evaluate daytime sleepiness, which was observed to be maximal in the morning, with a tendency for greater alertness as the day progressed [6]. Thorpy et al. concluded that "the reduced amount of REM sleep during the weekdays plus the tendency for sleepiness in the mornings may contribute to the behavioral and educational difficulties seen in these patients." The sleep pattern described in these individuals was that of sleep restriction on "school nights" and extreme sleeping in at weekends, in theory to "catch up".

The wide variation in wake time between weekends and school nights typically observed in DSPS has no correlates in other animals. Furthermore, younger school-aged children tend to fall asleep and wake up at similar times at weekends compared with school days. In the author's clinical experience it is unusual for children aged 8–9 years to sleep in at weekends to the degree often seen in teenagers. It is possible the initial clinical manifestation of DSPS is sleeping in at weekends.

The DSPS sleep pattern does not correlate with our social rhythm. Due to apparent intrinsic factors discussed later, the teenager with DSPS has greater difficulty shifting from a weekend sleep pattern to a school night pattern than his or her non-DSPS peers.

The ability to experience refreshing sleep is a key factor in a pure case of DSPS; if a teenager does not report waking refreshed after sleeping for several days on a stable schedule of his or her own choosing, a comorbid condition should, in the author's experience, be suspected. Sleeping late at a weekend may not provide sufficient time to establish whether or not sleep is truly refreshing. Furthermore, it is crucial for everybody, but teenagers in particular, to realize that chronic sleep restriction over five weekday nights cannot, in the author's opinion, be "made up for" over a 2-day weekend.

Epidemiology of sleep-onset insomnia

The main feature of DSPS is sleep-onset insomnia, a common disorder among teenagers, and DSPS should be included in the differential diagnosis whenever an adolescent is evaluated for these symptoms.

The first epidemiological study of insomnia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria [7], in US adolescents collected data from a random sample of 1014 teenagers aged 13–16 years in Detroit (MI, USA) [8]. Lifetime prevalence of insomnia was 10.7%, median age at insomnia onset was 11 years, and a total of 88% of teenagers with a history of insomnia reported current insomnia. The results also highlighted a predominately sleep-onset pattern of insomnia. Of those with insomnia, 52.8% suffered a comorbid psychiatric disorder.

In exploratory analyses of insomnia and pubertal development, onset of menses was associated with a 2.75-fold increased risk of insomnia. Before menses onset, the risk of insomnia was similar between girls and boys – a gender difference only emerged after this event. The authors concluded that insomnia was common and chronic among teenagers, and that the gender difference for insomnia risk emerged after menses onset [8].

DSPS and depression

DSPS is associated with depression and should be considered when evaluating teenagers with this disorder [6,9,10]. Researchers in Japan attempted to define the psychological features of patients with DSPS using a series of neuropsychiatric tests, including the Minnesota Multiphasic Personality Inventory (MMPI) and the Rorschach Inkblot Test [10]. Patients with DSPS manifested increased nervousness, depression, and difficulty regulating emotional displays when compared with a control group without insomnia or psychiatric symptoms, and were defensive, compulsive, introspective, and overly abstract in their thinking. They also tended to set high standards for intellectual achievement despite questionable cognitive ability, making them vulnerable to disappointment. Furthermore, they were impulsive and sought immediate gratification. The investigators described individuals with DSPS as likely to be neurotic, hypochondriac, depressed, and prone to conversion symptomatology, and suggested that these characteristics could increase social withdrawal, in turn decreasing the social cues that might entrain circadian rhythm, and ultimately making sleep phase shift more difficult.

Broad generalizations made from the results of a single study should be avoided; however, it is important to consider any factors that may influence the motivation of DSPS patients to modify their behavior. Changing sleeping habits can be challenging, and, in the author's experience, the incentive to improve sleep patterns may not be as profound in patients with DSPS compared with those without the condition. As with most chronic conditions, a vicious circle is often constituted.

Developmental changes in sleep patterns

Adolescent development is accompanied by profound changes in the timing and proportions of sleep and wakefulness. According to Carskadon, "As children mature into and through adolescence, their need for sleep does not decline substantially, although the opportunity to sleep is limited by lifestyle choices, academic […] schedules, and compelling changes in the biological processes" [11]. These

changes, she says, "include a more 'permissive' pace for the accumulation of sleep pressure across the day in older adolescents and a longer day length in the more mature. These factors all favor later bedtimes and rising times as children pass into adolescence, and a concomitant delay in the optimal timing for waking activities" [11].

Long-term longitudinal data have been published by Iglowstein et al. to illustrate the developmental course and age-specific variability of sleep patterns [12]. As part of the Zurich Longitudinal Studies, 493 children were followed using structured questionnaires to assess sleep at the ages of 1, 3, 6, 9, 12, 18, and 24 months, and then at annual intervals until the age of 16 years. Average total sleep duration at 6 months of age was 14.2 h/day (standard deviation [SD] 1.9 h/day) , which decreased to 8.1 h/day (SD 0.8 h/day) at 16 years of age.

The published findings strongly indicate that self-reported shortened total sleep time, variable sleep–wake schedules, late bedtimes and rising times, and poor sleep quality are negatively associated with academic performance for adolescents, from middle school through the college years [13]. Furthermore, children with sleep disorders frequently underperform in school [14].

A question commonly posed by parents is "how much sleep does my child need?" However, in the author's opinion, the focus should not be solely on the timing or quantity of sleep; ultimately, the overall quality must be considered. If a teenager is getting enough good-quality sleep at an appropriate circadian time, he or she should awaken spontaneously feeling refreshed. "Ideal sleep" can be simply described as the ability to fall asleep easily, sleep through the night, and wake feeling refreshed, without relying on hypnotics.

Why are teenagers particularly prone to DSPS?

The sleep patterns of teenagers differ from those of children and adults. Younger children may nap prior to bedtime and are unlikely to stay awake after their parents have gone to sleep, whereas teenagers may be allowed to remain up after their parents have retired for the night and frequently spend hours awake in their bedroom. In the author's clinical experience, it is very unusual for a younger child to sleep late at weekends; they tend to have similar bedtimes and rising times on weekdays compared with weekends, often varying by <1 h. A similar pattern is seen in adults.

In contrast, teenagers may have large differences between their bedtimes and rising times depending on the day of the week. Sleeping in and getting out of bed several hours later at weekends seems, in the author's experience, to be common practice. This may be due to a combination of external societal influences and physiological changes. Extensive research on adolescent sleep has been undertaken in the US [13,15–17], and the external influences on a teenager's sleep are numerous and pervasive.

For example, parents may not be teaching children to value sleep sufficiently. Parents may consider children well behaved if they remain quietly in their own bedroom. When children are small they may be punished by being sent to their bedroom early, or as a reward they may be allowed to stay up later; late bedtimes are worn as "badges of honor". In the author's experience, even small children may realize that their parents have later bedtimes than they do. As the child gets older a later bedtime at weekends may be allowed, perhaps reinforcing the message that staying up at night is good.

When children enter their teenage years, the levels of school work and extracurricular activities expected of them increase. The teenager is generally given more autonomy and the bedtime schedule is often further relaxed. Sleep is simply less of a priority. Since the teenager is becoming more adult, parents may incorrectly assume that he or she needs less sleep. It is increasingly apparent that adolescence may be a time of heightened sleep need coupled with a natural tendency to stay awake later [13,18,19]. As they get older, teenagers may stay up after their parents are in bed, therefore being allowed to set their own bedtime. Teenagers often want greater freedom, and what better opportunity when they are in their homes than when their parents are asleep? Therefore, teenagers have a number of incentives to stay awake later.

Genetics and DSPS

Although external societal influences undoubtedly have a role in teenage sleep patterns, physiological factors also appear to make a significant contribution. Patients with DSPS describe themselves as "night owls", and the preference for "eveningness" appears to run in families [20,21].

Several genes have been identified that may have a possible role in DSPS. Mammalian circadian rhythmicity has been shown to be regulated at the genetic level by transcription–translation feedback loops. Key molecular components are proteins including Clock, Timeless, and Period (Per) [21–26]. For example, a single nucleotide polymorphism of the human *CLOCK* gene has been shown to be related to diurnal preference; individuals carrying one of the two *CLOCK* alleles showed a strong preference for eveningness in a study by Katzenberg et al. [21].

There are three subtypes of the Per protein. UK-based researchers have reported a trend for the shorter allele of the length polymorphism in *PER3* to be strongly associated with eveningness (75% of the subjects with DSPS were homozygous for this polymorphism), whereas the longer

Table 1. SELF correction – a behavioral approach to the management of delayed sleep phase syndrome.

S: social interactions
E: exercise
L: light exposure
F: food intake

allele was associated with "morningness" [23]. A different molecular mechanism for DSPS has been reported by investigators in Japan, who identified a polymorphism in the gene for a rate-limiting enzyme, arylalkylamine *N*-acetyltransferase, utilized in the synthesis of melatonin [22]. They suggested this could be a susceptibility gene for DSPS.

Treatment of DSPS

Sleep problems in teenagers can present a challenging situation, both for the family and the primary care provider (PCP). The PCP may have limited training in pediatric sleep disorders, and in the author's experience the manifestation and management of DSPS will depend on the child's age, educational level, and overall family situation. In general, behavioral techniques should be the mainstay of treatment, although medications may have a role as an adjunct therapy in the management of insomnia.

Once a clinician suspects DSPS, diagnosis is not difficult; however, there can be many problems in obtaining a satisfactory response to treatment. Both behavioral and pharmacological methods have been employed, either separately or in combination, to treat DSPS, but attempts to correct the sleep schedule will not be effective unless the patient chooses to alter lifestyle factors influencing the delayed bedtimes, particularly at weekends [27]. The importance of motivation can not be overemphasized.

One of the benefits of a behavioral treatment approach is the ability of an individual to gain control over his or her sleep, with greater autonomy acquired as the condition improves. A mnemonic this author finds helpful in explaining a behavioral approach is "SELF correction" (Table 1). By keeping social interactions, exercise, light exposure, and food intake on a regular schedule, the circadian pattern will stabilize over time.

Non-pharmacological treatments for DSPS

Chronotherapy was originally suggested for the treatment of DSPS [2,28]. Chronotherapy resets the patient's sleep cycle using a series of consecutive, 3-h delay adjustments of bedtime and wake time over several days. To maintain the readjusted sleep pattern, the patient is encouraged to strictly adhere to the new sleep onset and wake times every day of the week, including weekends. However, this treatment can be impractical, as the progressive forward bedtime shifts will involve the patient temporarily sleeping in the daytime, and constant supervision must be ensured to prevent him or her sleeping at the wrong time. This treatment, although physiologically sound, therefore presents difficulties in its execution.

Another technique, phototherapy, resets the sleep–wake rhythm using bright morning light combined with evening light restriction to phase-advance the patient's sleep time [27, 29–31]. Phototherapy is based on the principle that bright light in the morning, at the end of the habitual sleep period, can phase-advance the circadian clock and hence wake onset, while bright light in the evening can phase-delay the circadian clock and sleep onset. Different phototherapy protocols have been used with varying success, and a pragmatic approach for the individual patient must be developed in each case. However, the technique should not be used in patients who are bipolar, as it may aggravate mania [27].

It has been suggested that patients with DSPS are particularly susceptible to the effects of evening light. A study by Aoki et al. reported that the suppressive effect of light on melatonin concentration was significantly greater in patients with DSPS than in control subjects [32]. The results indicate a hypersensitivity to nighttime light exposure in the condition, and further reinforce the importance of evening light restriction in patients with DSPS.

The practice at Stanford Sleep Disorders Center (Stanford, CA, USA) is to use a light intensity of 10 000 lux for 30–45 min immediately after awakening, over a period of several weeks. In addition, bright lights should be minimized in the last 2 h before the expected sleep time, including restricting the use of computer monitors. A practical compromise in teenagers may be to minimize or restrict the use of computers before bedtime, but to allow their use promptly after awakening, therefore serving as an incentive for the adolescent to get up on time or early.

Pharmacological treatments for DSPS

Treatment of patients with insomnia using melatonin has been described in a number of recent studies [33–38]. Melatonin is a hormone secreted by the pineal gland and its primary function appears to be the conveyance of information concerning the changing length of the night over the course of the year. According to Arendt et al., this information is used by photoperiodic animals to "ensure the correct timing of seasonally variable functions such as reproduction, coat growth, and probably the duration and organization of sleep" [39].

Melatonin has been used to treat poor sleep in a variety of conditions, including Asperger syndrome [32,33]. The timing

of the dose must be individually determined, based on the subject's core body temperature rhythm. Melatonin is an over-the-counter product and therefore does not have the same degree of regulation as prescription pharmaceuticals. This lack of regulation may cause the quality of over-the-counter melatonin to be highly variable [40].

A novel melatonin agonist, ramelteon, has recently been approved by the US Food and Drug Administration (FDA) for the treatment of sleep-onset insomnia in adults [41]. Although ramelteon may, in theory, help re-entrain circadian rhythms, to date there are no published data available on its efficacy or safety in teenagers with DSPS.

Other hypnotics are also available for the treatment of DSPS, but there is limited information on specific agents and, currently, there are no hypnotics approved by the FDA for use in teenagers. If a hypnotic were to be offered, it should be on the understanding that although it may provide immediate relief to the sleep-onset insomnia component of DSPS, long-term success will be ideally obtained with behavioral modification. In choosing a hypnotic, it is also preferable to use an agent with a short half-life to avoid next-day sedation. In the author's experience, hypnotics are often used incorrectly by teenagers and should, in general, be avoided for the treatment of DSPS [42].

Conclusion

With the variety of social and academic pressures placed upon teenagers, avoiding going to bed at an earlier time is an easy option, and a large difference between bedtimes and wake times on school nights compared with at weekends can reinforce the delayed sleep phase. The patient's motivation to modify his or her lifestyle is therefore essential for the successful treatment of DSPS.

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LEADING ARTICLE

The Impact of Sleep Apnea on Fatigue: Assessment Issues for Clinical Practice

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The obstructive sleep apnea syndrome (OSAS) is a common medical disorder. The condition is characterized by sleep-disordered breathing, with arousals from apneas and hypopneas leading to sleep fragmentation and ensuing fatigue. Night sweats and morning headaches are among the accompanying symptoms, with daytime sleepiness being the most predominant. Given the prevalence of fatigue in OSAS patients and its negative consequences on daily functioning and quality of life, its identification in these individuals is of great importance. This is of particular relevance in those for whom fatigue persists despite treatment of OSAS, as this can indicate that the OSAS is not the main or only cause. It is therefore vital to have a good understanding of the overlap between fatigue and related constructs, such as sleepiness and depression, and to use a valid and reliable instrument that is not confounded by these constructs and OSAS severity with which to identify patients at high risk of fatigue. Knowledge of the prevalence of fatigue in patients with OSAS and its determinants is important for secondary prevention in order to identify patients at risk of adverse secondary outcomes such as clinical depression, impaired quality of life, loss of productivity at work, and an increased risk of motor vehicle accidents. *Int J Sleep Wakefulness* 2007;**1**(2):66–9.

The obstructive sleep apnea syndrome (OSAS) is a common medical condition, with an estimated prevalence of 2–4% in middle-aged men and 1–2% in women, although prevalence rates vary between studies [1,2]. However, given that the definition of OSAS is continually evolving, these prevalence rates may neither be robust nor reflect the actual number of patients with OSAS. In addition, OSAS is generally under-diagnosed and under-treated, and it is estimated that up to 5% of the adult population in Western countries has undiagnosed OSAS [1]. This figure was confirmed in a recent analysis of data from the Sleep in America 2005 Poll undertaken by the National Sleep Foundation, which showed that one in four individuals from a representative sample of US adults would be considered high-risk candidates for a diagnosis of OSAS [3].

Hence, the prevalence and incidence of OSAS are likely to increase in the future as a result of the increasing elderly population and the rise in obesity that is expected to take on epidemic proportions. Risk factors for the development of OSAS include increasing age at least up to 65 years, obesity, male sex (with a 2:1 ratio), and craniofacial and upper-airway abnormalities [1,4]. Genetics, smoking, menopause, and nasal congestion are possible risk factors, but further studies are warranted to confirm their potential role in OSAS [1,4].

OSAS is characterized by sleep-disordered breathing, with arousals from apneas and hypopneas leading to sleep fragmentation and ensuing fatigue [1]. Associated symptoms comprise sweating during the night and morning headaches, with daytime sleepiness being the most predominant symptom. In addition, OSAS may lead to adverse secondary outcomes including:

- Clinical depression [5].
- Impaired quality of life [1].
- Loss in work productivity [6].
- Increased risk of car accidents [7].

Moreover, OSAS has been associated with the following more serious health outcomes:

- Hypertension [8].
- Glucose intolerance [9].
- Cardiovascular disease and mortality [10,11].

It is important to pay specific attention to fatigue in relation to OSAS as it may be an invalidating symptom that can be reduced with an adequate intervention. However, if OSAS is not the only or major cause of the fatigue reported by patients, this complaint will still have a major impact on patients' lives

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even after adequate treatment for the OSAS. Therefore, the focus of the current article is to evaluate the impact of OSAS on fatigue, to identify the overlap between fatigue and related constructs such as sleepiness and depression, and to provide recommendations as to how fatigue can best be assessed in patients with OSAS in clinical practice.

Fatigue, sleepiness, and related symptoms

Daytime sleepiness is a cardinal feature of OSAS that is often used interchangeably with fatigue because patients frequently complain of symptoms of both conditions. Although sleepiness, which reflects a physiological need for sleep, can be objectively quantified with tests, measurements of fatigue are more elusive and rely almost exclusively on self-report [12]. It is possible that this is the reason why fatigue in OSAS tends to have been assessed as a sub-component of quality of life rather than in its own right [13,14]. Given that fatigue is also included within the diagnostic criteria for major depression, as listed in the *Diagnostic and Statistical Manual of Mental Disorders IV – text revision*, this only adds to its complexity. A final problem is OSAS severity, which may serve as a confounder in this puzzle.

Some attempts have been made to disentangle this complexity and tease out the relative influence of sleepiness, mood, and presence of OSAS on fatigue. Indeed, some studies suggest that depression rather than severity of OSAS may explain fatigue in sufferers [12,15]. In addition, fatigue and sleepiness seem to be two independent constructs [16], indicating that the level of fatigue cannot be inferred by measures of sleepiness but should be assessed in its own right. A number of complaints, such as somnolence, are inherent to OSAS. When OSAS is treated, syndrome-specific complaints will also disappear. However, fatigue can have multiple causes, with OSAS being only one of them. For clinical practice, knowledge of the prevalence of fatigue in patients with OSAS and its determinants is important for secondary prevention in order to identify those patients at risk of adverse secondary outcomes, such as clinical depression [5], impaired quality of life [1], loss of productivity at work [6], and increased risk of motor vehicle accidents [7]. For this purpose, it is particularly important to have a valid and reliable scale with which to assess fatigue in the context of OSAS that is not confounded by disease severity and symptoms of depression.

Dimensionality of fatigue

Initially, fatigue was seen as a unidimensional construct [17], but the current perception is that fatigue is a multidimensional construct [18–20], divided into physical and mental components [21]. However, there is no consensus about this distinction, and support for the multidimensionality concept has been derived predominantly from statistical criteria that often overestimate the number of dimensions or assume multidimensionality in testing several models [22].

Some researchers have questioned the putative superiority of a multidimensional structure of fatigue [22–27]. Michielsen and colleagues examined the dimensionality of four existing fatigue measures and found strong support for the unidimensionality of the questionnaires used [22]. Unidimensionality of fatigue measures was not only found among healthy persons [22,27], but also in patients with sarcoidosis [25], breast cancer [28], and chronic pain [26]. This suggests that fatigue can be assessed adequately in terms of general fatigue.

Measuring of fatigue

Friedberg and Jason [13], and Alberts et al. [14] reviewed several questionnaires available for measuring fatigue in subjects with chronic fatigue syndrome [13], and in several populations with different diseases and the general population [14]. The majority have been developed for specific patient groups or ill persons in general, with the Fatigue Scale being one of the few developed for use in both hospital and community populations [21]. Generally, multidimensional fatigue scales are seen as more comprehensive and hence more adequate for providing a complete description of the patient's fatigue experience [14]. They are able to take into consideration that persons with the same overall score may differ substantially in their experience [20]. However, a disadvantage of multidimensional scales is the length of time they take to complete. Fatigue is frequently measured using subscales of broader measures; the Energy and Fatigue facet of the World Health Organization Quality of Life assessment instrument (WHOQOL-100) is a good example of this [29]. Recently, Dittner, Wessely, and Brown described 30 existing fatigue questionnaires [30]. This included information on the psychometric properties of the questionnaires and illustrations of their use. They provided recommendations for the selection of a fatigue scale for clinicians and researchers.

The Fatigue Assessment Scale

The Fatigue Assessment Scale (FAS), a short, valid, reliable, and easy to administer unidimensional fatigue questionnaire, was developed a few years ago [22,24]. The initial item pool from which it was developed comprised 40 items taken from four commonly used fatigue questionnaires:

- The Fatigue Scale [20].
- The Checklist Individual Strength [31].
- The Emotional Exhaustion subscale of the Maslach Burnout Inventory [32].
- The Energy and Fatigue scale of the WHOQOL-100 [29].

Several steps, described by Michielsen and colleagues, resulted in the final 10-item FAS, which can be used to quantify chronic fatigue [22,24]. First, items from the four fatigue questionnaires were removed that (i) could only be completed by specific groups (e.g. workers), (ii) were asking two questions at the same time, or (iii) were not obvious fatigue items. Second, a semantical procedure that was also used by the WHOQOL Group [33] was followed to reduce the 40-item pool. This procedure entailed a content analysis of the questions to identify semantically equivalent questions. Third, any questions that were substandard to the construct fatigue were deleted. Questions were then carefully grouped into categories asking about a similar type of fatigue. Judgements of semantical equivalence and categories were carried out by consensual agreement of two researchers. After the semantical analysis, the item per semantical group with the highest factor loading on the one-factor solution of the 40 items was chosen. In addition, an extra item concerning mental exhaustion was included. The reason for adding this item was to ensure that the most often represented domains of fatigue, mental and physical fatigue, were assessed in the same manner [21].

In the test phase, the FAS demonstrated good reliability and content validity [22]. Two subsequent studies among healthy persons showed the scale has a high internal consistency. Factor analysis and correlations confirmed the convergent and divergent validities. Indeed, using a higher-order factor analysis, the FAS had the highest factor loading on a one-factor solution when five fatigue questionnaires were included in the analysis [22,27]. Moreover, factor analysis revealed that fatigue, depression, and emotional stability are three separate constructs [22]. The authors examined whether the questionnaire should be scored differently for men and women and found that gender bias did not play a role in scoring of the FAS [22]. Studies among patients with sarcoidosis [25,34] and breast cancer [28] provided similar findings.

The psychometric properties of FAS were recently examined in 94 patients with OSAS (apnea–hypopnea index [AHI] 35±26 events/h) from the Antwerp University Hospital (Antwerp, Belgium), and a gender (77 males), age (51 years), and body mass index (29.3) matched control group with non-apneic snoring or mild OSAS (AHI ≤15 events/h). The association between fatigue, as measured using the FAS, and sleepiness was examined [35]. Besides the FAS, patients completed the Epworth Sleepiness Scale [36], the Neuroticism–Extraversion–Openness Five-Factor Inventory [37], the Beck Depression Inventory [38], the Global Mood Scale [39], and the Short-Form Health Survey (SF-36) [40], a general health status scale, prior to diagnosis. Factor analysis showed the FAS to be a unidimensional scale that measures one concept in patients with OSAS and their controls. Moreover, the internal consistency of the FAS was good (Cronbach alpha coefficient 0.92). Patients with OSAS experienced more fatigue than the matched controls, but there were no differences regarding sleepiness. The correlation coefficient between fatigue and sleepiness was 0.54. Both fatigue and sleepiness correlated strongly with the SF-36 vitality scale (r=–0.84 and –0.95, respectively). Additionally, fatigue was strongly associated with neuroticism (0.54), depression (0.70), and negative affect (0.83; $p<0.001$ for all) [35].

Conclusion

There is evidence to suggest that fatigue should be studied in its own right in patients with OSAS. The FAS, a brief, valid, and reliable instrument, the utility of which has recently been demonstrated in patients with OSAS [35], may be a helpful instrument in the continuing attempts to further disentangle the potential overlap between disease severity, sleepiness, depression, and fatigue in the context of OSAS. One advantage of the FAS in the context of this condition is that it is not confounded by somatic symptoms and is independent of depression. Additional properties of the FAS that should be examined in OSAS patients are test–retest reliability, sensitivity to change, and criterion validity. Future, large-scale prospective studies of patients with fatigue are warranted in order to investigate the relative influence of OSAS severity, sleepiness, and depression on fatigue.

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LEADING ARTICLE

Bringing Medical Products to Market in the United States: A Condensed Review for Clinical Investigators

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The world of sponsored, regulated clinical research is complex, and the task of understanding the responsibilities and the ethical nuances of conducting research lies with the investigator. Using the US as an example, this article will review regulatory requirements, explain the difference between pharmaceutical and medical device research, and discuss marketing application options. It will focus on the importance and limitations of ethical responsibilities in obtaining consent from research participants. *Int J Sleep Wakefulness* 2007;**1**(2):70–7.

As clinicians, we place our trust in the approval processes through which medical products are brought to market. However, given recent product withdrawals (e.g. the nonsteroidal anti-inflammatory drug rofecoxib withdrawn by Merck & Co, Inc. [Whitehouse Station, NJ, USA]) and recalls (e.g. the Boston Scientific Corporation [San Diego, CA, USA] recall of guide catheters), failure to protect human participants during trials, and scientific fraud, our trust in this system has been undermined and replaced with feelings of doubt and skepticism [1–4]. However, no alternative system currently exists for the commercialization of medical products, and we must therefore continue to rely on governing agencies such as the US Food and Drug Administration (FDA) to approve medical products that are safe and effective for the market.

The roles of the FDA, investigator, sponsor, and research institution

Commercialization of a medical product, whether a medical device or a pharmaceutical product (see Table 1 for definitions), remains an arduous and expensive process, with the collection of clinical data being one of the most costly activities. Bringing a medical product to market requires a team approach, with each member having a specific role. Throughout the product development process, "checks and balances" accompany each level of interdependence to ensure that each entity meets its obligations.

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The US FDA reviews clinical data provided by a research sponsor in order to substantiate its product claims. This is true for all pharmaceuticals and some medical devices and biologics (biological products include, for example, vaccines, allergenics, and blood components). The sponsor of the research is dependent on the abilities and the ethical principles of the clinical investigator to provide data that are free from bias, ethically collected, and meet the regulatory requirements of the FDA. In addition to the investigator, the research institution has an important role. Academic medical centers are most frequently used for industry-sponsored research. Each institution has institutional review boards (IRBs) that work with an investigator to ensure the conduct of responsible research.

The investigator is defined by the FDA as the "individual who actually conducts a clinical investigation" [6,7] (Table 2). In this context, the investigator is directed by the sponsor, who typically drafts the protocol, and determines the endpoints and subject selection criteria. Often, this is done with input from the investigator. It would be difficult for the sponsor to meet scientific and regulatory commitments without the investigator, and the investigator therefore plays a crucial role in the product development process, in conjunction with his or her respective institution.

A particular set of skills and specific knowledge are needed to be a good investigator. The investigator must be familiar with the products and current standards of practice within his or her field and, when deciding to participate in a trial as an investigator, it is critical to consider such issues in order to make a qualified choice. The investigator and site staff must be willing to abide by the ethical and regulatory

Table 1. Definitions of medical products (adapted from the US Federal Food, Drug and Cosmetic Act [5])

- Drugs are defined as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease […] and […] articles (other than food) intended to affect the structure or any function of the body of man or other animals" [5].
- A medical device is defined as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is […] intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or […] intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body […] and which is not dependent upon being metabolized for the achievement of any its primary intended purposes" [5].

Table 2. US Food and Drug Administration definitions of parties involved in the drug development process (taken from [6]).

- Investigator means an individual who actually conducts a clinical investigation (i.e. under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.
- Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.
- Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

requirements for human subject protection, and to ensure that the research is conducted in accordance with good clinical practices. The investigator acts as the moral and scientific "compass" for the sponsor and patient participants alike, and must appreciate that he or she also represents the public's interest and safety.

Since 1906, regulations have been in place that aim to ensure the provision of safe food and drugs. Sweeping changes occurred in 1938 with the introduction of the Federal Food, Drug, and Cosmetic Act (FDC Act) [8]. The Act established a more rigorous process for the development and marketing of medical products. In 1976, the medical device sector underwent major changes with the introduction of the Medical Device Amendments to the Act, which require premarket FDA review of all such products [9].

As amendments to the original FDC Act are constantly being made in response to changes in technology and the medical climate, it is essential that an investigator is aware of any changes impacting his or her participation. The FDA website (www.fda.gov) is the first port of call for learning more about the regulations and expectations regarding investigators.

Although the ethical, legal, and scientific considerations are similar for the pharmaceutical and medical device product development processes, the route of bringing a product to market differs.

Within the FDA, different offices exist that have expertise in the specific product categories. These are:

- The Center for Drug Evaluation and Research.
- The Center for Device and Radiological Health.
- The Center for Biologic Evaluation and Research.

With the advent of technology that combines novel drug delivery systems, a new office, the Office of Combination Products, was created in 2002. Each center has its own organizational structure lending the scientific and regulatory expertise needed to provide safe and efficacious products.

Product development: pharmaceuticals

Preclinical testing phase

The purpose of the preclinical testing phase is to assess the biological safety of a product in laboratory and in animal studies. This component of the process typically takes 3–5 years. If the results of the preclinical phase are compelling, an investigational new drug (IND) application is filed with the FDA using form 1571.

The IND application does not allow the sponsor to market the drug, but allows it to be shipped for investigational purposes by allowing exemptions from certain regulatory requirements. The IND application is sectioned into three components:

- Animal pharmacology and toxicology studies.
- Manufacturing information.
- Information regarding the clinical trial and investigator.

After submission of the IND application, the sponsor or investigator must wait a minimum of 30 days before beginning a study. If the investigator or sponsor has not heard back from the FDA after 30 days, he or she can decide to begin the study. However, in most cases the reviewing branch will contact the sponsor with approval or questions prior to the end of the reviewing period [10].

Clinical testing

Phase I

Phase I testing is the first "in-human" assessment that takes place during drug development. The purpose is to determine the drugs' safety and dosage in healthy volunteers. Patients can also be enrolled in this phase of testing, particularly where treatments for potentially fatal conditions are concerned. Phase I studies also collect metabolic data regarding pharmacokinetics and pharmacodynamics. Pharmacokinetics explores the effect of the body on the drug, whereas pharmacodynamics investigates the effect of the drug on the body.

The trial size is small at this stage, usually including 20–80 subjects, who are closely medically monitored within a well-staffed clinical research center. A protocol for Phase I can be more flexible than that of Phase II or III [11,12].

Phase II

The next phase of the process is an evaluation of the product's efficacy and the development of a profile of any side effects. This stage lasts approximately 2 years and typically involves the study of several hundred patient volunteers [11,12].

Phase III

Trials in this phase are the largest of all of the premarket studies, involving thousands of patient volunteers to collect further safety and effectiveness data. This phase allows the manufacturer to formulate labeling. Due to large study size, the data can be generalized [11].

Phase IV

Phase IV studies are done in the post-marketing or commercialization stage of development, and are typically required by the US FDA to increase understanding of the drugs' safety and to assess long-term adverse events. A manufacturer will often conduct the study without a request from the FDA in order to obtain pharmacoeconomic data or to a study a new comparator [11,12].

Product development: medical devices

Compared with pharmaceuticals, medical devices require a notably different approach to commercialization. Depending on its characteristics, a device can be submitted for approval by the US FDA for marketing in one of three ways:

- Premarket notification (known as the "510[k] process").
- Premarket approval (PMA).
- Product development protocol.

Medical devices are classified by the FDA as being class I, II, or III devices. Classification is risk based with class I representing the lowest and class III the highest risk. Most class I devices are exempt from 510(k), but still require certain criteria be met, such as establishment registration and general quality system requirement controls.

The majority of devices fall into class II and thus require a submission to the FDA prior to marketing, using the premarket notification or 510(k) process. Using this process, the FDA clears a product for marketing based on substantial equivalence to a device that is already available. This does not mean that the product is identical, rather that certain characteristics are similar enough such that, along with general and special controls, its safe and effective use can be assured. Only a small minority of premarket notifications have a requirement for inclusion of clinical data.

Class III products almost always require clinical data submission and a PMA application in order to obtain marketing clearance. A device that falls into this category does not have enough safety or effectiveness information available to ensure that it will not cause undue harm [13].

Clinical trials for medical devices are not specifically differentiated into phases. Similar to the IND process, medical devices can be tested in investigational device exemption studies. The FDA separates device studies into those with significant or non-significant risk. A non-significant risk study has abbreviated requirements compared with a significant risk study. It requires only IRB review prior to study initiation, whereas a significant risk study requires both FDA and IRB review. Risk evaluation is based not only on the device, but also on procedures and the patient population [14]. While the process is different, the goal is the same – to ethically and scientifically provide data in order to substantiate that a product is safe and effective.

The ethics of clinical research

An investigator has many responsibilities in the conduct of research; however, ensuring the rights and wellbeing of the subjects involved should be of the highest priority. In addition, the investigator is responsible for the ethical conduct of the trial and proper record keeping.

Human participant protection

How does the investigator provide the appropriate balance between risk and benefit? There are many documents that set forth the ethical principles for conducting research in order to help him or her make decisions. Some of the more

important documents of which the investigator should be aware are summarized below:

- Drafted in 1947, in response to the horrendous experiments on prisoners during World War II, the Nuremburg Code outlined basic principles of human research. The first statement of the code is that the voluntary consent of an individual to participate is essential [15].
- The World Medical Association created its official policy document regarding human research in 1964, The Declaration of Helsinki. There are a number of basic principles for all medical research described therein, with additional standards for clinical research combined with clinical care. This document has been revised numerous times, the most recent revision being in 2000, and several clarifications have been made, the last of which was 2004 [16]. Other organization, such as the Council for International Organizations of Medical Sciences [17], also provide standards documentation.
- In 1996, in an effort to improve consistency among pharmaceutical trials conducted within and outside of the US, the International Conference on Harmonisation developed its guideline for Good Clinical Practices (ICH E6) [18]. ICH E6 outlines the ethical and scientific standards required for good clinical practice. The goal of the document was to ensure that clinical trial data used in the drug approval process are standardized worldwide. In addition to this, compliance with the document ensures that the protection of human subjects is maintained. Currently, this document is more specific to pharmaceutical, rather than medical device, development; however, the foundation recommendations for the conduct of clinical trials can be transferred to the medical device arena.

These documents provide the principles by which research should be conducted within the global research community. They recognize the need for research to enhance the lives of people as a whole, but not at the expense of the individual research participants.

In 1974, the then President of the US signed into law the National Research Act, under which the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed. The commission was charged with describing the boundaries between clinical practice and research, and defined ethical considerations regarding human participant research. The output from the Commission's meetings was the Belmont Report, which describes clinical practice as concern about a single individual's diagnosis and treatment, while research is conducted to contribute to generalizable knowledge for the "good of mankind" (Table 3) [19].

Table 3. Ethical tenets of the Belmont Report [19].

Respect for persons: "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection".

Beneficence: "Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being".

Justice: This tenet relates to fair distribution of the risks and benefits of research. However, depending on the type of research, certain groups may be excluded, and therefore the exclusions must make scientific and ethical sense, and, as much as possible, equal distribution should occur. The Belmont Report states that "There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed".

These formulations are:

- "To each person an equal share".
- "To each person according to individual need".
- "To each person according to individual effort".
- "To each person according to societal contribution".
- "To each person according to merit".

The investigator must carefully consider the principles given in Table 3 as defined within the report, as the terms themselves carry a different meaning when used in the context of clinical research. For instance, the term "justice" in the Belmont Report means "fairness in distribution", signifying that risk and benefits should be equal across the spectrum of humanity (for example, the poor should not bear the burden of research while the wealthy receive the benefit). According to the Merriam-Webster dictionary, justice means being "impartial" or "fair", and this context, while similar, does not take into account the complexity of performing clinical research [20].

A periodic review of these documents and theories is therefore necessary for the clinical investigator as a reminder of the ethical principles of research, and how these should be applied.

Clinical equipoise

Research always involves a balance between the risks and the benefits of conducting a trial. This balance must be considered for each participant. An investigator must also believe that there is uncertainty as to whether a certain product will perform better than others. This is termed "clinical equipoise", or, sometimes, the "principle of uncertainty".

The concept of clinical equipoise relates to the "general" population of clinicians. It represents the collective thinking of

Table 4. US Codes of Federal Regulations associated with clinical research.

CFR name*	CFR description
45 CFR 46	Department of Health and Human Services policy for protection of human research participants
21 CFR 50	Protection of human participants
21 CFR 54	Financial disclosure
21 CFR 56	Institutional review boards
21 CFR 312	Investigational new drug application
21 CFR 314	Applications to market new drug
21 CFR 812	Investigational device exemption
21 CFR 814	Premarket approval of medical devices

*CFR names given in format "[CFR title number] CFR [part number]".

the group. For instance, disagreement as to whether drug "A" is better than drug "B" enables an investigator to ethically decide whether or not participation makes sense [21].

The uncertainty principle takes a more individualized approach, and considers a single investigator's belief that he or she is not certain which treatment arm would be better for an individual patient. The key points are that, regardless of the random assignment, participants will not unduly suffer harm, and furthermore that the results of the experiment cannot be predicted [22].

Responsibilities of investigators

Regardless of whether involved in the development of a drug or device, the FDA requires that the investigator signs a contract that outlines what is expected of him or her and establishes his or her qualifications. For drug research, the investigator signs FDA form 1572. In a device study, there is no specific FDA form, although the investigator is required to sign an agreement with the sponsor. The general and specific responsibilities of the investigator are detailed in the respective Codes of Federal Regulations (CFRs; Table 4). In addition, the sponsor may have added responsibilities specific to a product or clinical trial. It is the responsibility of the investigator to understand what is required and to agree to conduct the study as detailed in the agreements (Table 5).

Informed consent process

The Institute of Medicine's 2004 report *Health Literacy: A Prescription to End Confusion* states that "over 90 million Americans have difficulty understanding and using health information" [25,26]. In other words we, as healthcare professionals, often do not perform particularly well in adequately explaining the healthcare material given to a large proportion of the population.

Table 5. Responsibilities of investigators during the development of pharmaceuticals and medical devices.

- General responsibilities of investigators during new drug development, according to 21 CFR 312, Subpart D, Section 312.60 [23]:
  "An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter".
- General responsibilities of investigators of medical devices, according to 21 CFR 812, Subpart E, Section 812.100 [24]:
  "An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G".

CFR: Code of Federal Regulations; FDA: Food and Drug Administration.

The definition of healthcare literacy used by Healthy People 2010 [27] is "the degree to which individuals have the capacity to obtain, process and understand basic health information and services to make appropriate health decisions" [26].

As well as an individual's capabilities, the concept of healthcare literacy also includes the context in which information is delivered, and takes into account the cultural components and language barriers that may be present in understanding health materials. Furthermore, it should be considered that an individual's level of education does not necessarily reflect his or her level of understanding [28]. The American Medical Association (AMA) provides information that may offer useful suggestions for improving health literature [29]. The US Department of Health And Human Services Office of Disease Prevention and Health Promotion also offers suggestions and tools for helping individuals to understand healthcare material [30].

Poor health literacy poses an additional burden to the research team in that participating in a study may not provide any benefit to an individual subject, and the unique research vocabulary required adds to the complexity of written materials.

It cannot therefore be assumed that potential subjects understand at the onset of a trial, and thereafter maintain an understanding of, the nuances of informed consent throughout their research participation.

The informed consent process is verbal, written, and ongoing. It begins when any member of the research team speaks to a potential participant, or when a recruitment advertisement is read and the process continues throughout a participant's "time on study". The signing of the consent form may not necessarily mean that a participant actually comprehends the material, and frequent and ongoing communication is therefore essential to ensure understanding.

The understanding of informed consent by a study participant is an important issue as the literature confirms that most consent forms exceed the language capabilities of the participant, and furthermore that research subjects often do not comprehend the supporting documentation they are provided with [31].

Although not stated as a necessary ethical component of recruitment by guidelines, one must appreciate what drives an individual patient to participate in a clinical trial. This information helps the investigative team to assess the balance between risk and benefit, and should not be taken lightly. Motivational reasons for participating in a clinical trial are as individual as the participants themselves. The investigator or the investigative team should discuss motivation with the potential participant during the consenting process.

Written informed consent must also conform to the regulatory requirements described in the CFR for products that require review from the FDA. Furthermore, the elements of informed consent and the limitations in obtaining it are described in CFR Title 21 Part 50 – Protection of Human Subjects [32].

Informed consent violations are frequently cited in FDA warning letters [33], which can be a good source of information for investigators wanting to learn what not to do. In addition, if the infraction is severe enough, an investigator can be barred from conducting further research.

Several lawsuits have been brought against institutions, most notably the University of South Florida (Tampa, FL, USA) and the Fred Hutchinson Cancer Research Center (Seattle, WA, USA), regarding informed consent; these should be learnt from. Developing readable and understandable informed consents is a risk management strategy for an institution involved in research. The investigative team should conduct a thorough review and analysis of the informed consent as part of the research process.

Record keeping

The investigator, his or her staff, or both, are responsible for maintaining appropriate records. The expectations of the FDA in terms of record keeping are described in the relevant CFRs. Non-compliance with record keeping is another of the most frequently cited issues in FDA warning letters [34]. Appropriate record keeping provides evidence that a trial was conducted according to the protocol, that informed consent was achieved, and that adequate oversight by the IRB was maintained. It also provides documentation regarding receipt, distribution, and other disposition of the investigational product. For a complete appreciation of the record keeping requirements within a research center, it is recommended that current and future investigators review the regulations and develop a standard operating procedure to ensure that record keeping is satisfactory.

The IRB

The investigator and the sponsor rely on the IRB to approve their research. It is therefore imperative that the IRB conducts itself according to the relevant regulations. In the recent past, the temporary shutting down of several IRBs for failure to adequately review and maintain records has re-iterated this point. The primary responsibility of the IRB is to ensure that the safety and well being of the subject is protected. This includes review of any advertising or recruitment materials. The IRB is a FDA-regulated entity and as such, must be compliant with its specific regulation, CFR Title 21 Part 56, which describes the required structure and function of the IRB in detail [35].

An IRB has the authority to approve, approve with modifications, or disapprove all research activities. Typically, the sponsor communicates with the IRB via the investigator, but it is not specifically prohibited for a sponsor to interact with the IRB without the investigator. As the agreement to conduct a trial is between the sponsor and the investigator, it remains the investigator's responsibility to ensure that the reviewing IRB meets the regulatory requirements. One way is to check whether the institution's IRB has a federal wide assurance. If the investigator is unsure, he or she can consult with the IRB or check its listing on the website for the Office for Human Research Protections [36].

The FDA has the jurisdiction to conduct audits of an IRB and sanctions can be imposed. If an IRB is found to be non-compliant, there are a number of actions that may occur, including IRB closure, the halting of enrollment in ongoing studies, the inability of the IRB to approve additional research, or, ultimately, disqualification of the IRB. Other actions, such as criminal or civil actions, may also be taken against the IRB or its parent institution.

An IRB can obtain accreditation through the Association for the Accreditation of Human Research Protection Programs and a list of accredited IRBs can be obtained from the Association's website (http://www.aahrpp.org/www.aspx).

Reports

The investigator is also responsible for reporting back to the sponsor or FDA. As interim or progress reports are required to be filed to the FDA by the sponsor, the investigator must submit them to the sponsor in a timely fashion. Final reports are also required for the submission of the marketing application. In addition, the "prompt" reporting of adverse events is required. For example, the FDA requires reporting "as soon as possible but in no event later than 15 calendar days after the sponsor's initial receipt of the information" for a serious or unexpected life-threatening experience associated with a drug [37].

All of these responsibilities and requirements dictate that the investigator has a hands-on approach to the everyday running of the clinical trial, and to ensuring that it is correctly administrated. Having knowledgeable, ethical, and committed ancillary help is crucial to maintaining compliance with good clinical practices.

Budget negotiation

Budget negotiation for the both the sponsor and investigative site is important. Industry-sponsored work often keeps research programs funded in times when governmental funding is not available and, with proper negotiation, the trial site can attain sufficient revenue to stay open. While not part of the clinical trials process, budgeting and negotiating remains an important aspect of moving a product through the research phase and into the market. The site should negotiate a fair price for tests and clinic visits, properly calculate salaries of staff, and include overhead costs, which range from 15–35% depending on the geographical location (see [38] for an example). Overheads are not typically negotiable, but certainly influence the sponsor's bottom line.

To certify or not?

The complexities in the conduct of clinical trials of regulated products means there is a growing movement to certify investigators. The industry of clinical research is becoming more complex and competitive, and few clinicians at this time are able to obtain regulated research training during their course work. Sponsors are looking for investigative sites that can provide effective subject recruitment, can conduct trials according to good clinical practices, and are responsive to various forms of communication.

A sponsor cannot afford to work with an investigator and site that may be found in non-compliance during an audit. Since the mid-1990s, clinical research associates and coordinators have had the ability to become certified; it therefore makes sense for the investigator to also attain certification. Several organizations offer certification and, in addition, many major academic medical centers offer such courses, some as graduate medical education. At a minimum, most research-oriented academic medical centers, and many sponsors, require that an investigator take courses in human subject protection.

Summary

The worldwide clinical trials business is a multi-billion dollar industry. In 2001, the annual industry spend on contract clinical services was estimated to be nearly US$10 billion [39]. Industry sponsors, whether for pharmaceuticals or medical devices, are on strict timetables to get their product to market. They cannot "take a chance" on a contract research organization or site not fulfilling its obligations in a timely manner.

Clinical research is an intricate "ballet" of regulations, ethics, coordination, and responsibilities. The investigator must continually be aware of any changes in regulations that may impact the running of clinical trials. Ensuring that his or her investigative site meets all of the sponsors' and regulatory requirements is paramount to continuing good clinical practice and encouraging repeat business opportunities.

The informed consent process must be the top priority for everyone involved in a clinical trial. Understanding the underlying issues regarding health literacy and personal motivation may aid the investigator in enrolling subjects. Furthermore, the investigator should be well versed in associated responsibilities regarding record keeping and the IRB, not forgetting his or her accountability to ensure that the board meets regulatory requirements.

The process of getting a medical product to market is rigorous and depends on the collective team working together in an effort to improve the health of the public. Without willing and ethical investigators and staff, individuals who agree to participate in research, and regulatory bodies, the provision of safe and effective medical products would be impossible.

Disclosures

Robyn Woidtke is also the Senior Manager for Clinical Affairs with Ventus Medical Inc.

Suggested reading

US FDA guidance documents for good clinical practice and the conduct of clinical research can be found at http://www.fda.gov/oc/gcp/guidance.html.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

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

NARCOLEPSY

Modafinil-induced hippocampal activation in narcolepsy

Kim YK, Yoon IY, Shin YK et al.
Neurosci Lett 2007;**422**:91–6.

The precise mechanism of action of the wakefulness-promoting agent modafinil in the management of daytime-sleepiness disorders such as narcolepsy is, as yet, unknown. This article describes a study in which the effects of the drug on cerebral glucose metabolism in different regions of the brain were characterized using positron emission tomography in participants with narcolepsy. Compared with pre-treatment scans, the investigators noted a significant increase in glucose metabolism in the left hippocampus upon administration of modafinil, thus offering an insight into the drug's mode of action.

Imaging studies have recently been performed in an effort to characterize potential structural and functional changes in the brains of people with narcolepsy (see [1] for an example), a chronic disorder involving daytime sleepiness. The wakefulness-promoting agent modafinil is used in the management of this symptom in narcolepsy and idiopathic hypersomnia; however, its mode of action remains unknown. While exploratory investigations of modafinil's effects on the brain have been performed on brain slices or in animals (for example [2]), the authors of the present study claim that theirs is the first to assess cerebral metabolic changes in patients with narcolepsy.

Six females and two males with narcolepsy (mean age 16.4 years, age range 15–18 years) were recruited to the study. All participants complained of excessive daytime sleepiness, and all exhibited a mean sleep latency of <8 min upon multiple sleep latency testing. Modafinil treatment was commenced at a dose of 100 mg each morning, with doses increased to a maximum of 400 mg if required. The effects of the drug on daytime sleepiness were assessed using the Epworth Sleepiness Scale and a visual analogue scale.

Brain metabolism in these patients was investigated before and after two weeks' treatment with modafinil using [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET). FDG PET scans were initially compared with those of eight healthy volunteers (six females and two males, mean age 21.6 years, age range 20–23 years) to investigate metabolic abnormalities associated with narcolepsy, and subsequently the differences between pre- and post-modafinil scans in the narcoleptic patients were evaluated.

The investigators found that, compared with those of healthy volunteers, pre-treatment FDG PET scans of narcoleptic patients exhibited significantly reduced glucose metabolism in various brain regions, including the bilateral hypothalamus, thalamus, midbrain and upper pons, and hippocampus (all p values ≤0.001). The statistical significance of these differences in metabolism was reduced, or became non-significant, for several brain regions when scans from post-treatment narcoleptic patients and healthy controls were compared. The investigators noted a statistically significant increase in left hippocampal glucose metabolism after modafinil administration when comparing pre- and post-treatment scans in the narcoleptic patients ($p<0.005$). There was also a trend towards increased metabolism in the hypothalamus and midbrain, among other regions.

These findings suggest that modafinil stimulates the hippocampus, a region of the brain that receives afferents from the hypothalamus, in patients with narcolepsy. While additional, larger studies are necessary to confirm these results and further explore the action of the drug, this study is the first to identify narcoleptic brain metabolism changes after modafinil administration.

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SLEEP-DISORDERED BREATHING

The effects of 1-year treatment with a Herbst mandibular advancement splint on obstructive sleep apnea, oxidative stress, and endothelial function

Itzhaki S, Dorchin H, Clark G et al.
Chest 2007;**131**:740–9.

The authors of this study examined the use of a Herbst mandibular advancement splint (MAS) as an alternative treatment for mild obstructive sleep apnea (OSA). The findings indicate that Herbst MAS was a moderately effective treatment for OSA, with good rates of compliance.

It is imperative that patients with obstructive sleep apnea (OSA) receive proper treatment for their disorder due to the severe implications of not only comorbid disorders and increased risk for cardiovascular disease, but also the daytime impairments that are often present, such as excessive daytime sleepiness. Currently, nasal continuous positive airway pressure (nCPAP) therapy is the standard treatment for OSA, but due to the poor nCPAP compliance rates among the OSA patient population, investigation into other treatments that may have improved rates of compliance is vital.

The study group comprised patients diagnosed with sleep apnea using polysomnography who had declined the use of nightly nCPAP therapy. A total of 12 OSA patients from the initial study group of 16 completed the 1-year follow-up evaluation. A further six untreated individuals with OSA served as a control group, and 10 subjects without OSA were assessed as a reference group. All were matched for age, gender, body mass index, and comorbidites. Study subjects had forward jaw protrusion and healthy teeth. Exclusion criteria included alcohol abuse and any narcotic or psychiatric drug use. A cast model was made of the jaw, and the mandibular advancement splint (MAS) adjusted so that the allowable protrusion (75% of maximum) was obtained. Changes in apnea–hypopnea index (AHI), oxygen desaturation index, and subjective reports were assessed.

At the 1-year follow-up, results showed that the study group had a significant decrease in mean AHI from baseline (29.7 events/h vs. 19.6 events/h; $p<0.005$), although the reduced AHI index scores were still higher than those in the reference group. There were no significant changes in AHI scores in the control group. Patients receiving the MAS had significant reductions in AHI at all evaluation points (2 weeks, 3 months, and 1 year). Subjective sleepiness was also significantly decreased from baseline at the 1-year follow-up in subjects receiving the MAS compared with the control group.

Previous studies have reported the use of MAS to cause comparable reductions in AHI scores and sleepiness to those seen in subjects treated with nCPAP. Although the size of this study sample was small, OSA parameters improved with the use of MAS and compliance rates were better than those observed for nCPAP. For OSA patients who refuse nCPAP therapy, MAS appears to be a suitable alternative treatment.

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Maintenance of wakefulness test as a predictor of driving performance in patients with untreated obstructive sleep apnea

Sagaspe P, Taillar J, Chaumet G et al.
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The principal aim of this study was to determine whether the Maintenance of Wakefulness Test (MWT) is an accurate predictor of driving performance in patients with untreated obstructive sleep apnea (OSA). This study comprised 30 men with untreated OSA who underwent polysomnography, the MWT, and simulated driving for 1 h. Measurements included mean sleep latency, Epworth Sleepiness Scale (ESS) score, and standard deviations from the center of the road on the driving stimulator. Results revealed that an abnormal MWT with mean sleep latency (0–19 min) was associated with simulated driving impairments, whereas there was no correlation between driving impairments and ESS score, apnea–hypopnea index, microarousal index, or total sleep time.

Although the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test (MWT) have become established as objective measures of sleepiness and wakefulness, no rigorous testing has been performed outside a laboratory setting to determine their relevance to real life situations. The MWT is considered an objective measure for assessing an individuals' ability to remain awake in soporific conditions. Since sleepiness when driving is recognized as a critical factor in motor vehicle accidents, the authors of the present study investigated whether the MWT can predict driving performance in patients with untreated sleep-disordered breathing events, such as obstructive sleep apnea (OSA).

Thirty men with untreated OSA participated in the study. Subjects had a mean age of 51±8 years, a mean body mass index (BMI) of 29±3, and a mean apnea–hypopnea index (AHI) of 43±24. Each patient underwent one night of polysomnography (PSG), four 40-min MWT trials, and 1 h of simulated driving that was assessed through the standard deviation from center of the road on the driving

simulator (SDS). Patients were then classified into three groups based on their results on the MWT:

- Sleepy (0–19 min).
- Alert (20–33 min).
- Fully alert (34–40 min).

Individuals with sleep disorders other than OSA were excluded on the basis of the PSG. Each subject also completed an Epworth Sleepiness Scale (ESS) to determine their perceived level of daytime sleepiness. The mean sleep latency on the MWT inversely correlated with body mass index, AHI, and age. Fully alert patients performed better on the driving simulator than those in the other groups ($p<0.01$), reflecting the inverse correlation between mean MWT score and SDS. Interestingly, and somewhat bafflingly, the driving performances of those with mean MWT scores of 20–33 min did not significantly differ from the other two groups.

Previous studies have predicted that BMI and AHI are strong predictors of objective daytime hypersomnolence in patients with OSA, and this study lends strength to the association by including SDS as another criterion to assess performance and sleepiness. Limitations of this study include the small number of participants, the male-only subjects, and the lack of exclusion of other medical conditions besides OSA that may have skewed the data. The authors concede that biases – including the performance ability of the participants on the driving simulator, which does not replicate actual driving conditions – belie the consequences that could ensue from poor performance in this "real" setting.

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Association of alcohol consumption and sleep disordered breathing in men and women

Peppard PE, Austin D, Brown RL et al.
J Clin Sleep Med 2007;**3**:265–70.

Although most studies examining the relationship between the acute administration of alcohol and sleep-disordered breathing (SDB) events have found a deleterious effect, the association between SDB and moderate, chronic alcohol consumption has not been determined. The aim of this population-based epidemiological study was to investigate whether chronic habitual alcohol use has an effect on SDB. Data suggested that, in men, increased alcohol consumption incrementally contributes to a worsening of SBD, regardless of the temporal proximity to sleep while in women no such relationship exists.

In previous studies, acute administration of alcohol prior to bedtime has been associated with a worsening of sleep-disordered breathing (SDB) events, namely more frequent and lengthened hypopneic and apneic events. Alcohol is known to initiate and/or exacerbate these breathing events by reducing upper airway patency through a decrease in muscular tone. The authors of the present study investigated whether the consumption of mild to moderate levels of alcohol, regardless of the time of day, would lead to a similar worsening of SDB events. Participants who reported >5 years of chronic drinking habits, defined as an average of up to six drinks per day, were randomly selected from the Wisconsin Sleep Cohort Study. To minimize the acuity of alcohol administration, no more than two drinks were allowed during the night of the polysomnography (PSG).

A total of 1420 participants (775 men and 645 women) were evaluated with nocturnal PSGs and subjectively assessed with questionnaires detailing their alcoholic habits in addition to other confounding variables such as smoking, body mass index (BMI), and use of medications. After adjusting for such variables, analysis revealed that, for men, each incremental drink per day resulted in an approximately 25% increase in the odds of SDB. However, no significant associations were found between male alcohol consumption and the odds of moderate or severe SDB (defined as apnea–hypopnea index [AHI] >15 events/h). Interestingly, no significant associations were observed between mild to moderate consumption of alcohol and SDB in women. Beer accounted for approximately 61% and 32% of alcoholic drinks in men and women, respectively, and was significantly associated with mild to more severe SDB (AHI >5 events/h).

Based on the above data, the authors recommend that those who are susceptible to SDB should minimize their alcohol consumption, regardless of temporal proximity to bedtime. The insignificant associations between alcohol consumption and the odds of moderate or severe SDB could not be accounted for by the authors, but they suggest that this may be the result of the small sample size of patients with severe SDB or a ceiling effect – perhaps alcohol can initiate SDB events but not impact on existing, mild SDB. The non-significant association between alcohol use and SDB in women is harder to explain, but the authors suggest that it is possible that moderate alcohol consumption is not fully accounted for as fewer than 10% of the women reported an average of one or more drinks per day. Alternatively, it is possible that hormonal and anatomical differences between men and women could also account for this difference.

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Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial

Richards D, Bartlett DJ, Wong K et al.
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Recognizing the poor level of continuous positive airway pressure (CPAP) compliance among patients with obstructive sleep apnea (OSA), the authors of this study attempted to determine whether cognitive–behavioral therapy (CBT) would increase CPAP adherence. OSA patients, aged 32–81 years (n=100), were subjected to either a CBT intervention followed by a treatment-as-usual approach or solely to the latter. An assessment of CPAP usage (hours) was made on night 7 and 28. Adherence was significantly greater in the CBT group than in the treatment-as-usual group at both day 7 and 28, highlighting the efficacy of CBT as a rational and cost-effective method for increasing CPAP usage.

Previous studies have illustrated that long-term continuous positive airway pressure (CPAP) compliance by obstructive sleep apnea (OSA) patients is predicated by the ability of CPAP to provide symptomatic relief in addition to its successful initial use. Only a handful of studies have assessed behavioral interventions designed to increase CPAP usage with little information on those refusing treatment prior to CPAP titration. The authors of this study attempted to broach both of these issues by determining whether a cognitive–behavioral therapy (CBT) intervention can improve adherence to CPAP and influence treatment decisions before CPAP titration.

The 100 participants (96 males) aged 32–81 years were diagnosed with obstructive sleep apnea (OSA) and randomized to receive either a CBT intervention or treatment as usual. Adherence to CPAP was assessed at nights 7 and 28 The two CBT interventions (each lasting 1 h) included slide presentations, videos, and demonstrations of simple relaxation strategies to emphasize the perceptions, expectations, and self-efficacy of CPAP for the treatment of OSA and the medical consequences of declining treatment. All participants underwent one treatment-as-usual group education session that emphasized the CPAP titration process and the possible side-effects. Mean number of hours of CPAP use at 28 days was used as the primary outcome measure, with secondary measures including the mean usage at 7 days and the number of patients adhering to treatment at both time points (defined as ≥4 h of nightly use).

The two groups did not differ with regard to sex, age, body mass index, respiratory disturbance index, Epworth Sleepiness Scale scores, or Depression Anxiety and Stress Scale scores. At 28 days, CPAP was used for 2.9 h per night more in the CBT group than in the treatment-as-usual group ($p<0.0001$). Furthermore, 37 members of the CBT group (77%) were adhering to CPAP at the 28-days timepoint compared with just 31% in the other group. Data collected at day 7 revealed similar findings, with 88% adherence in the CBT group and 39% in the treatment-as-usual group. The rate of CPAP refusal, either before or after the titration study, was 8% and 30% in the CBT and treatment-as-usual groups, respectively. Those in the CBT group also had higher scores for self-efficacy and social support, as determined by questionnaires.

This study highlights the efficacy of CBT for improved CPAP adherence, especially given that CBT is cost-effective and simple, at least as applied in this study. Limitations of the study include the lack of long-term follow-up, as well as the lack of a true placebo group. Since the success of a CBT approach can be dependent on the socioeconomic status of the patient, this factor also needs to be taken into account. The disparity of sexes is also an issue that necessitates further research.

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Obstructive sleep apnea is associated with increased urinary albumin excretion

Faulx MD, Storfer-Isser M, Kirchner HL et al.
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Further to the association of urinary albumin excretion with endothelial pathology and its significance as a predictor of cardiovascular disease, the authors of this study attempted to elucidate its role in obstructive sleep apnea (OSA). A total of 496 adults with various degrees of OSA underwent nocturnal polysomnography and urinary collection to determine whether an association exists between apnea–hypopnea index and albumin-to-creatinine ration (aACR). The authors conclude that there is a significant correlation between increased urinary albumin excretion and OSA, especially in its more severe form, and this may explain the association of OSA with cardiovascular disease.

Although there is an established association between obstructive sleep apnea (OSA) and cardiovascular disease, the pathophysiology underlying this relationship is difficult to ascertain. Since albuminuria reflects endothelial dysfunction linked to cardiovascular events, it is assumed that there is a direct correlation between OSA and microalbuminuria in individuals with intact glomerular filtration. Therefore, the present authors investigated the relationship between OSA severity and the albumin-to-creatinine ratio (aACR).

The study was completed by 496 participants who had a family member diagnosed with OSA. Subjects were required to undergo a polysomnography (PSG) and give urine samples. The authors also collected medical histories using questionnaires, took blood pressure readings, and performed various other physiological assessments. OSA was defined using the apnea–hypopnea index (AHI) and aACR was adjusted for both race- and sex-associated variation in creatinine excretion. Since 172 subjects were hypertensive and 63 had diabetes, two-way interactions between AHI and both diabetes and hypertension were evaluated. Results revealed a great variability in the AHI of the participants, with 47% having an AHI score <5 events/h, 23.4% with mild OSA (AHI 5–14), 14.7% with moderate (AHI 15–29), and 14.9% in the severe range (AHI ≥30). Those harboring a severe form of OSA were predominantly male, older, heavier, and more likely to have diabetes or hypertension than those without OSA or with milder forms of the condition. There was a good correlation between aACR and AHI, with a higher aACR in those with a severe OSA. The highest prevalence of microalbuminuria was observed in those with the most severe form of OSA – these subjects also had a significantly lower glomerular filtration rate than those in the AHI <5 group.

This study suggests that the presence of severe OSA is significantly associated with an increased level of urinary albumin excretion even after adjustments for diabetes, hypertension, and obesity. As the authors surmise, this increased excretion could theoretically be secondary to sleep-related pathology, such as intermittent hypoxemia and increased sympathetic tone, which, in turn could serve as markers for cardiovascular disease (CVD). Furthermore, after secondary adjustments for diabetes and hypertension, the increased urinary aACR levels observed in the subjects may be due to the OSA itself. Since an increased urinary aACR suggests endothelial dysfunction and is correlated with severe OSA, this subset of patients may benefit from both closer medical supervision and pharmacotherapy to target the microalbuminuria. Although this study may have a number of clinical implications, the effect of hypertension and diabetes on albuminuria is not conclusively differentiated from that of severe OSA.

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Redefining success in airway surgery for obstructive sleep apnea: a meta-analysis and synthesis of the evidence

Elshaug AG, Moss JR, Southcott AM et al.
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This review attempts to gauge the efficacy of surgery for obstructive sleep apnea, a topic that has been heavily debated throughout the years. The authors propose that the "success" surgery confers be posed in terms of effective results; that is, a post-surgical apnea–hypopnea index (AHI) of ≤5 events/h sleep.

The viability and efficacy of surgery for obstructive sleep apnea (OSA) has often been debated. A recent review claimed successful outcomes in 35–62% of patients [1]. Although the traditional definition of "success" in the surgical literature is a reduction in the apnea–hypopnea index (AHI) score of ≥50%, this does not necessarily support a successful outcome as this level of reduction may not be clinically, albeit statistically, significant. In the present meta-analysis, the authors reviewed 18 studies, including 17 with level 4 evidence (case series) to examine the results of surgical methods, such as Phase I and II procedures, and ultimately develop a novel and more appropriate definition of success.

The authors extracted AHI scores from the selected studies and categorized them into varying degrees of success:

- Either a ≥50% reduction in the post-surgical AHI, an AHI of ≤20 events/h, or both.
- Post-surgical AHI of ≤10 events/h.
- Post-surgical AHI of ≤5 events/h.

Under the traditional definition of success, patients who underwent Phase I procedures, including soft palate surgery, hyoid suspension, and genioglossus advancement, had a pooled success rate of 55%. This was reduced to 31.5% if success was defined as a post-surgical AHI ≤10 events/h, and reduced further to 13% for an AHI ≤5 events/h. The success rates were significantly better for Phase II procedures (predominantly mandibular and maxillary advancements), but still low considering the extent of these surgeries. The traditional definition of a ≥50% reduction in AHI score yielded a pooled success rate of 86%; however, when success was considered to be a post-surgical AHI score of ≤10 or ≤5 events/h, the pooled success rates were 45% and 43%, respectively.

As the authors acknowledged, this meta-analysis has a number of shortcomings, mainly with regard to the heterogeneity of the various studies. For example, follow-up time from surgery to polysomnography (PSG) varied from 6 weeks to 12.3 months. Body positions and sleep stages during the PSG that yielded these particular AHI scores are also not described, but may be a significant factor for those with positional-dependent apneas and hypopneas. Furthermore, pre- and post-surgery body mass indexes, which could further confound results, were not stringently recorded in every study. Success rates for the various procedures were not

individualized but amassed together. Given the variability of the surgeries themselves, this could further skew results although this poses less of a problem for the Phase II procedures, which have less procedural heterogeneity. Nevertheless, despite the many pitfalls inherent in this type of meta-analysis, the authors suggest that the definition of success in airway surgery for OSA be amended to allow for clinical, rather than just statistical, significance, as this will have implications for both policy and practice.

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INSOMNIA

Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial

Edinger JD, Wohlgemuth WK, Radtke RA et al.
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Pharmacotherapy is the most common treatment for insomnia and although cognitive–behavioral therapy (CBT) has also been shown to be an efficacious treatment, the perceived time required to administer CBT has limited its use in the clinical setting. The authors of this study aimed to determine the number of CBT treatment sessions required to achieve optimum results in patients with insomnia. Those subjects who received four treatment sessions over an 8-week period had the highest rate of response. However, additional studies are needed to determine the optimal treatment regimen of CBT for insomnia.

Cognitive–behavioral therapy (CBT) is well-established as an effective treatment for insomnia but, despite this, its use in clinical practice has been limited. The length of time and level of training required for CBT are often cited as reasons to explain this discrepancy. However, prior to this study, no evaluations had been performed to determine the number of treatment sessions required to achieve the optimal therapeutic effect. Typically, CBT for insomnia involves a primary consultation followed by a series of visits that address barriers to effective implementation. These follow-up visits contribute significantly to the cost of treatment. The authors of the current study intended to address this problem by examining the dose-response effects of CBT for insomnia and evaluating the minimum number of treatment sessions necessary to achieve optimal therapeutic effects.

The study comprised 86 subjects with primary sleep-maintenance insomnia who were randomized to receive either one (week 1), two (week 1 and week 5), four (fortnightly), or eight (weekly) treatment sessions over the course of 8 weeks. Patient outcome was assessed using a sleep diary and actigraphy.

The results suggest superiority of the four-session treatment regimen. The group that received four sessions had the greatest percentage of clinically significant responders (58.3%) compared with the groups that received one, two, or eight sessions (response rates of 43.8%, 22.2%, and 35.3%, respectively). Furthermore, only the four-session group maintained the improvement in sleep efficiency, by both diary and actigraphic data, at the 6-month follow-up assessment.

These findings support the clinical use of CBT, administered in four sessions within an 8 week period, for the treatment of insomnia; however, further work is required to optimize the regimen. It is of interest that the therapeutic response was not proportional to the number of treatments. This could be due to a number of factors. For example, as well as the number of treatment sessions, the treatment interval varied between the regimens. Therefore, the superiority of the results of the fortnightly therapy could be a reflection of the efficacy of a 2-week inter-session interval, rather than the efficacy of four treatment sessions. While the findings of this study are a valuable contribution to the literature, perhaps its greatest value is in highlighting the need for future research to optimize the regimen of CBT for the treatment of insomnia.

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Asymptomatic insomnia

Schneider-Helmert D.
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Few studies of sleep-state misperception (or paradoxical insomnia, as it is now referred to in the *International Classification of Sleep Disorders*, 2nd edition) have been reported in recent literature; however, the number of such investigations are increasing. The current retrospective study examines sleep-state misperceptions in a patient population.

In this article, Schneider-Helmert refers to sleep-state misperception as asymptomatic insomnia, where no specific symptoms of insomnia, aside from daytime impairment, exist in the diagnosis. The majority of the patients in this retrospective study had been referred to the Kirschgarten Pain Clinic sleep center (Basel, Switzerland) on the basis of daytime impairment complaints in the absence of any sleep disturbance. A total of 27 patients, who had undergone

polysomnograph recordings for one night and completed a questionnaire the next morning about their night's sleep in the laboratory, were studied. Subjects varied with regard to their sleep and psychiatric disorders (including three patients with restless legs syndrome, two with light sleep apnea, six with pain syndromes, and six with psychiatric disorders). No subject was free of health problems.

The most significant finding was that the study population had mean sleep fragment duration – the time between spontaneous awakenings – of 21.5 min, indicating difficulty in sleep maintenance. Overall, the total sleep time was <5 h, while estimated sleep duration was 7.5 h. All other sleep parameters, such as sleep latency and distribution of sleep stages, were within normal ranges. Analysis of alpha sleep in the study population revealed that overestimation of total sleep time was greater in individuals with non-alpha sleep than in those with alpha sleep (mean and median 180.9 min and 154 min vs. 155.9 min and 136 min, respectively), although this difference was not statistically significant.

Interestingly, even when patients were shown their objective sleep results, they still did not believe themselves to have a sleep problem. A total of 14 patients accepted treatment for insomnia and follow-up showed not only a reduction in sleep disturbances, but also an improvement in daytime symptoms. The current study, along with previous reports, raise the possibility that asymptomatic insomnia is not being diagnosed in the clinical setting due to the lack of primary symptoms presented by the patient.

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Sleeping with the enemy: clock monitoring in the maintenance of insomnia

Tang NK, Anne Schmidt D, Harvey AG.
J Behav Ther Exp Psychiatry 2007;**38**:40–55.

There is evidence that pre-sleep worry plays an important role in insomnia for many affected individuals. The authors hypothesized that clock-watching is a trigger of pre-sleep worry and contributes to sleep difficulty, and report the results of two studies. In the first, self-reported "poor sleepers" and "good sleepers" were randomized to either monitor or not monitor the clock prior to sleep onset. In the second, individuals with primary insomnia were randomized to monitor either the clock or a display that contained data related to a control task. In both studies, those assigned to clock-watching reported greater sleep worry and a longer sleep latency. These findings support the hypothesis that clock-monitoring can trigger sleep-disruptive pre-sleep worry.

Excessive worry about sleep is an established characteristic of many insomnia patients and many individuals with this disorder attribute their difficulty falling asleep specifically to pre-sleep worry. The authors of the present study hypothesized that clock-watching behavior might be a trigger to excessive pre-sleep worry and the resultant sleep disturbance, and performed two studies to test this theory.

The first study included 60 individuals, 30 subjects who were not formally diagnosed with insomnia but characterized themselves as "poor sleepers", and 30 self-reported "good sleepers". Both groups were randomized to instruction to either monitor or not monitor the clock prior to falling sleep. Subjects were assessed using actigraphy, self-rated sleep-onset latency, and a 10-point Likert scale that recorded the degree to which an individual's worry about falling asleep interfered with their ability to do so. The results found that those randomized to clock-monitoring reported both increased worrying and a longer time taken to fall asleep.

Although the results of the first experiment were as expected with regard to clock-monitoring, there were two main limitations. The "poor sleepers" randomized to the non-monitoring group reported a lower than expected level of pre-sleep worry during the study. This group was selected because of their self-reported sleep disturbances, including a high level of pre-sleep worry. Although restriction of clock-monitoring could have relieved their worry, it is unknown whether the results from this cohort can be generalized to a wider insomnia sample without classification of their symptoms using standardized diagnostic criteria. Secondly, the clock-monitoring task required the subjects to keep their eyes open and process information, while those asked to not monitor the clock were not required to do either. To determine whether the observed differences were a specifically a result of clock-monitoring, a control task was required and the authors therefore performed a second experiment to address these limitations.

The second study comprised 38 formally diagnosed primary insomnia patients who were randomized to perform one of two tasks while attempting to fall asleep. The first was to monitor the clock and the second was to monitor a display that included data related to a control task, but no time information. The results seen were similar to those of the first study: individuals randomized to clock-watching reported more worry related to sleep and longer sleep latency.

These findings support the notion that clock-monitoring can trigger sleep disruptive pre-sleep worry. Future work based on these results should examine interventions that eliminate clock-watching among insomnia patients.

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Effects of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia

Van Der Heijden KB, Smits MG, Van Someren EJ et al.
J Am Acad Child Adolesc Psych 2007;**46**:233–41.

Children with attention-deficit/hyperactivity disorder (ADHD) frequently experience sleep-onset insomnia that is accompanied by a delayed increase in evening melatonin levels. This study is the first placebo-controlled evaluation of the efficacy and safety of melatonin in non-medicated children with ADHD and sleep-onset insomnia. The results showed that, compared with placebo, treatment with melatonin led to significantly earlier sleep onset, shorter sleep-onset latency, and greater total sleep time in non-medicated children with ADHD. However, no significant effects on behavior, cognition, or quality of life accompanied this improvement in sleep.

Sleep-onset insomnia is often seen in children with attention-deficit/hyperactivity disorder (ADHD). It has been estimated that one-third of medication-free children with ADHD have difficulties falling asleep [1,2].

The typical increase in endogenous melatonin levels that occurs in the evening is delayed in children with ADHD-associated sleep-onset insomnia compared with children with ADHD who do not show insomnia symptoms [3]. The occurrence of such a phase-delay in normal children has been shown to predict a stronger therapeutic sleep phase-normalizing effect in response to exogenous melatonin [4].

Several studies have demonstrated the efficacy and safety of melatonin therapy for sleep-onset insomnia in children with ADHD. However, these studies have only included children who were receiving medication for their disorder. Since the most common treatments for ADHD are stimulants, which themselves carry a significant risk of causing sleep-onset insomnia, the results could be due to the melatonin addressing a medication side-effect, rather than treating a primary sleep difficulty. This study by Van Der Heijden et al. is the first placebo-controlled evaluation of the efficacy and safety of melatonin in non-medicated children with ADHD and sleep-onset insomnia.

The authors randomized 105 medication-free children diagnosed with ADHD and chronic sleep-onset insomnia to receive 4 weeks of either melatonin (3 mg or 6 mg, depending on body weight) or placebo, taken nightly at 7 PM. No restrictions were placed on the bedtime of the participants, though an average sleep onset of later than 8:30 PM was required for entry into the study. Outcome was measured with actigraphy and sleep diaries. The authors found that melatonin treatment led to a significantly earlier sleep onset, shorter sleep-onset latency, and greater total sleep time than placebo. There were no significant adverse effects associated with melatonin therapy. However, the improvement in sleep was not accompanied by any significant effects on behavior, cognition, or quality of life, although this could be a reflection of the size of the therapeutic effect or an aspect of the study design.

This study concludes that melatonin treatment is safe and can improve sleep in children with ADHD. Future studies are required to determine whether this treatment can improve quality of life in this patient group.

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A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder

Carney CE, Segal ZV, Edinger JD et al.
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This study aimed to determine the number of post-treatment insomnia complaints in patients receiving either pharmacotherapy or cognitive–behavioral therapy for the treatment of major depressive disorder.

Although many studies have shown a close association between depression and insomnia, the pathophysiological pathways of sleep and depression are complex and not yet fully understood. The importance of treating depression and insomnia as separate disorders in order to reduce the likelihood of depression relapse has been highlighted by a number of recent trials. The current study adds to the literature on treatments for depression and their effect on symptoms of insomnia.

The trial was of a retrospective design with the clinical population drawn from a larger study investigating the outcomes of patients with major depressive disorder treated with either pharmacotherapy or cognitive–behavioral therapy (CBT). A total of 94 patients, who had completed 20 weeks of therapy and achieved depression remission as measured by the Hamilton Rating Scale for Depression (HAM-D), were enrolled. Subjects were aged 18–65 years, and those with a current diagnosis of bipolar disorder,

substance abuse disorder, schizophrenia, or borderline personality disorder were excluded from the study. The presence of a sleep disturbance was measured using the HAM-D. Patients randomized to the pharmacotherapy arm received antidepressants for 6 months based on the treating psychiatrist's clinical judgment while those in the CBT arm received 10–13 individual sessions, each 50 min in length, over a 26-week period.

Overall, both groups showed a decrease in sleep complaints post-treatment compared with the pretreatment period (sleep-onset insomnia 59% vs. 22%, sleep-maintenance insomnia 71% vs. 26%, and early morning awakenings 50% vs. 17%, respectively). However, comparisons of pre- and post-treatment insomnia status between the two therapy arms showed no significant differences.

Although the majority of the study population had resolution of their insomnia complaint post-treatment, a number of individuals continued to suffer sleep difficulties. This suggests that these two conventional forms of therapy do not address residual rates of insomnia following remission of depression. Therefore, it is important when caring for patients with depression and complaints of insomnia to ensure that both these disorders are treated.

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CIRCADIAN RHYTHM

Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life.

Erman MK, Rosenberg R; for the US Modafinil Shift Work Sleep Disorder Study Group.
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In this 12-week trial, the investigators assessed the effect of the wake-promoting agent modafinil on functioning and quality of life in 278 patients with excessive sleepiness associated with shift work sleep disorder. Modafinil's tolerability and effects on day- and night-time sleep were also assessed. The drug significantly improved functioning and quality of life in this patient group, was well tolerated, and was not associated with clinically meaningful changes in sleep parameters compared with placebo.

Shift work sleep disorder (SWSD), a circadian rhythm sleep condition, is becoming increasingly prevalent in our society and has been reported to affect 32% of night or rotation shift workers in the US [1]. The excessive sleepiness caused by SWSD can negatively impact on daily living, impairing an individual's performance and quality of life.

In the present study, the investigators performed a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effects of modafinil on patient functioning, health-related quality of life, and sleep in patients suffering from excessive sleepiness associated with SWSD. Between February 2001 and March 2002, a total of 278 outpatients, aged 18–60 years, were enrolled in the study from 31 centers in the US and randomized to receive modafinil 200 mg, modafinil 300 mg, or placebo, taken orally 30–60 min before the start of each night shift. Patient characteristics at baseline were similar for the three groups.

The Functional Outcomes of Sleep Questionnaire (FOSQ) and the 36-item Short-Form Health Survey (SF-36) were used to assess patient functioning and health-related quality of life, respectively. Subjects were also asked to keep daily diaries of day- and night-time sleep and caffeine consumption. Drug tolerability was monitored throughout the study and additional assessments, including routine clinical laboratory tests, were performed.

Modafinil 300 mg significantly improved patient functioning, as determined by an increase in mean FOSQ score from baseline to final assessment, compared with placebo (2.3 vs. 1.6-point increase; $p<0.05$). A similar effect was seen in patients receiving modafinil 200 mg compared with placebo; however, this did not reach statistical significance (2.0 vs. 1.6-point increase; $p>0.05$). Specifically, patients receiving modafinil 300 mg showed improved scores from baseline in the FOSQ domains of vigilance, activity, and productivity, compared with those given placebo.

Significant improvements in SF-36 mental component scores from baseline were also observed in both modafinil arms compared with placebo (mean changes of 3.7, 3.2, and 0.7 points in the modafinil 200 mg, modafinil 300 mg, and placebo groups, respectively). No clinically meaningful changes in sleep parameters or caffeine use were noted across the treatment groups.

The most commonly reported adverse events in patients receiving modafinil were headache (21.5%), nausea (12.4%), and nervousness (6.8%). These were reported as mild or moderate in 98% of cases. Overall, 28 patients withdrew from the study due to adverse events; five were receiving modafinil 200 mg, nineteen were taking modafinil 300 mg, and four were in the placebo group). One patient in the modafinil 300 mg group was withdrawn due to an abnormal liver function test result; liver enzymes normalized on cessation of treatment.

The study authors conclude that patients with excessive sleepiness due to SWSD who received modafinil over a 12-week period before the start of each night shift showed improvements in aspects of functional status and quality of life, as measured by the FOSQ and SF-36. Modafinil was well tolerated in this patient group and was not reported to affect intended sleep. Trials performed over longer study periods are required to fully determine the effect of modafinil on function and quality of life in patients with excessive sleepiness associated with SWSD.

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Association between sleep and morning testosterone levels in older men

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Although it is recognized that the circulating testosterone levels of men decrease with age, the role of sleep in this process has not been well analyzed. This study attempted to broach this issue by investigating whether the testosterone levels of healthy older men correlate with objective differences in their sleep patterns. Healthy men (n=12) aged 64–74 years underwent polysomnography, actigraphy monitoring, and measurements of total and free testosterone. The results revealed that the amount of nocturnal sleep was an independent predictor of the subjects' morning testosterone levels.

Given that waning testosterone levels have been linked to a variety of metabolic disorders and health consequences, the variability of these levels in older men is both confounding and of great clinical interest. Previous studies have illustrated the importance of a healthy sleep quantity and quality for increasing testosterone levels. The authors of the present study attempted to replicate these findings in a group of otherwise healthy older men whose sleep quantity and quality had been adversely affected by aging.

The study was completed by 12 healthy men, aged 64–74 years, who did not have any active medical or sleep disorders, such as clinically significant sleep-disordered breathing (SDB). The amount of nocturnal sleep was quantified through both actigraphy and polysomnography (PSG). Total and free testosterone levels were measured in fasting blood samples taken after a night of typical sleep quantity and quality. Regression analysis, controlling for respiratory disturbance index (RDI), age, and body mass index (BMI), was performed to examine the relationship between morning testosterone levels and actigraphy or PSG results.

Although considerable variation was found between the quantity and quality of participants' sleep, a significant positive correlation was identified between the average amount of nocturnal sleep and morning total testosterone levels (p=0.004). In contrast, there were no significant relationships between androgen levels and sleep onset or morning waking times. The results of the multiple regression analysis also demonstrate that total sleep time is an independent predictor of morning testosterone levels, despite the inclusion of RDI in the model.

The findings suggest that total sleep time may contribute to the augmentation of testosterone levels, and sleep efficiency and maintenance also play minor roles. Limitations of the study include the small sample size, which may not provide a true representation of the population of older healthy males. It is also unclear to what extent the authors account for the disruption of sleep and alteration of sleep architecture that occurs with aging and are not necessarily related to total sleep time and the other variables studied. Nevertheless, this study poses some interesting questions that warrant further investigation.

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MEETING REPORT

160th Annual Meeting of the American Psychiatric Association

San Diego, CA, USA, May 19–24, 2007

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Held during Mental Health America's "Mental Health Month", the 2007 American Psychiatric Association (APA) annual meeting took place in San Diego, CA, USA. The meeting, which according to the APA continues to be the largest gathering of psychiatric professionals anywhere in the world, this year focused on the theme of "Addressing Patient Needs: Access, Parity, and Humane Care". Over the course of the 6-day event, healthcare professional delegates from around the world had access to more than 1000 research papers, posters, symposia, and workshop sessions in San Diego Convention Center and its nearby hotels. A wide variety of mental health topics were discussed, including depression, schizophrenia, anxiety, addiction, ethics, and litigation. Sleep and wakefulness were also covered in a number of sessions, and the highlights of these are presented below.

Obstructive sleep apnea syndrome

Hyun Kwon Lee (Seoul National Mental Hospital, Seoul, Republic of Korea) presented low-resolution electromagnetic tomography (LORETA) imaging and electroencephalograph (EEG) data from 10 individuals with mild obstructive sleep apnea syndrome (OSAS) and 10 patients with severe OSAS. Participants were also screened with several psychometric scales, including the Epworth Sleepiness Scale (ESS) and the Beck Depression Inventory. The aim of the study was to identify regions of the brain associated with recurrent nocturnal hypoxia in OSAS.

The LORETA results showed reduced alpha activity in the right posterior cingulate gyrus in those with severe OSAS compared with those with mild OSAS ($p<0.05$). Absolute powers of alpha activity were reduced in several areas on EEG assessment in severe OSAS patients compared with those with the milder form of the disorder (p value for each brain area <0.05). These findings suggest that, in OSAS, repeated short-term hypoxias during sleep may lead to cortical brain dysfunction.

Sleep and mental health

Iwona Chelminski (Rhode Island Hospital, Providence, RI, USA) presented research on the diurnal preferences of patients with mental illness, particularly the "morningness–eveningness" dimension. Data from those previously screened for the Rhode Island MIDAS (Methods to Improve Diagnostic Assessment Services) project were included in this study. Specifically, 230 gastric surgery candidates (the control group) and 410 outpatients with psychiatric illness were included. Participants were categorized based on the presence or absence of depression and anxiety, and completed the Morningness–Eveningness Questionnaire (MEQ).

The study revealed that participants with psychiatric illness had a tendency towards eveningness in comparison with those in the control group. Those in subgroups with depression had a greater degree of eveningness and were more likely to be considered as an evening type on the MEQ than other participants. These data suggest that eveningness may suggest vulnerability to psychopathology in general, and depression in particular.

Dr Chelminski also presented information on the potential impact of seasonal changes in mood and behavior on diurnal preferences in patients with depression. A total of 410 people with depression screened for the MIDAS project were evaluated with the MEQ and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders. Data from these assessments were compared across two seasons of the year for 181 depressed patients in spring/summer and 93 depressed subjects in fall/winter.

Circadian types (evening, morning, or neither) were almost identically distributed across both seasons and MEQ scores did not differ between seasons. This finding suggests that the degree of eveningness does not change with the seasons in depressed patients.

Kyung-Kyu Lee (Dankook University Hospital, Cheonan, Republic of Korea) presented research on the quality of sleep in hemodialysis patients with chronic renal failure. Ninety-

two patients (52 male and 40 female) were screened with several sleep, depression, and quality of life scales, including the Pittsburg Sleep Quality Index (PSQI). Sixty-two participants were rated as poor sleepers on the PSQI (global score >5). These individuals had higher scores on depression and anxiety scales, and lower physical functioning, than those considered good sleepers (global PSQI score <5). These data suggest that hemodialysis patients with chronic renal failure have a high prevalence of poor sleep, which, in turn, results in lower quality of life in subjective measures.

Hypersomnia: background and management

Cephalon, Inc. supported a symposium entitled "Still Sleepy After All These Cures: Hypersomnia in Psychiatry". Stephen M Stahl (University of California, San Diego, CA, USA) opened the discussion with an introduction to hypersomnia, considering the condition in the context of depression, as a consequence of narcolepsy or behaviorally induced insufficient sleep syndrome, and as a side effect to medication.

He then went on to discuss the neurobiology of the condition, explaining that glutaminergic transmission in the reticular formation, tuberomammillary nucleus, basal forebrain, and posterior hypothalamus has been implicated in the symptomatology of hypersomnia. Other neurotransmitters shown to be involved in this disorder include dopamine, norepinephrine, and histamine. Activities in the locus coeruleus, midbrain raphe nuclei, anterior cingulated gyrus, and dorsolateral prefrontal cortex have also been implicated in the condition.

Daniel J Buysse (University of Pittsburgh School of Medicine, Pittsburgh, PA, USA) continued the symposium with a discussion on the clinical presentation of hypersomnia. While fatigue often presents with a physical sense of tiredness without the tendency to fall asleep, hypersomnia is characterized by excessive daytime sleepiness and the tendency to fall asleep at times when it is not ordinarily appropriate to do so. Around 5–10% of adults report hypersomnia, said Dr Buysse, and it is associated with several medical conditions, including cardiovascular disease. It is most commonly due to a lack of adequate sleep, which has many causes including OSAS and voluntary limitation of sleep duration. Hypersomnia may also be triggered by certain medical conditions (e.g. Parkinson's disease) and by psychiatric disorders such as depression. Some medications can also cause hypersomnia, including selective serotonin reuptake inhibitors.

Meeta Singh (Henry Ford Hospital, Detriot, MI, USA) continued the symposium with a presentation on the measurement of hypersomnia. Careful evaluation of the patient is necessary to ensure that the most appropriate diagnosis, and therefore treatment choice, is made. Measurement of hypersomnia usually begins with a clinical interview and can also involve certain sleep questionnaires, a sleep diary, and assessment with subjective psychometric scales such as the ESS and the Brief Fatigue Inventory. Objective measures of sleepiness include the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT). The MSLT can be helpful in exploring the likely cause and severity of sleepiness, while the MWT is useful in monitoring the patient's response to treatment.

In the penultimate presentation of the symposium, Leslie P Lundt (Foothills Foundation, Boise, ID, USA) discussed treatment options for hypersomnia. Sleep hygiene is often recommended, as is limiting smoking and alcohol use prior to going to bed. Improved nocturnal sleep can also be achieved with the use of hypnotic agents. Daytime hypersomnolence may be managed in part by using stimulant and nonstimulant medication. Several small studies (e.g. that by Bastuji and Jouvet [1]) suggest that the stimulant modafinil is effective in reducing hypersomnia and reduces drowsiness and sleep attacks.

Christopher L Drake (Henry Ford Hospital) concluded the symposium with a discussion of the consequences and prevalence of hypersomnia. Estimates of the prevalence of excessive daytime sleepiness range from 10% to 20% of the population. As well as being caused by disorders such as narcolepsy and OSAS, hypersomnia can result from several psychiatric conditions. For example, one study showed that of 215 outpatients using an antidepressant medication, 44% reported sleep disturbances and 38% reported fatigue [2]. These were the most common residual symptoms reported in this study and Dr Drake concluded that the presence of hypersomnia should trigger clinicians to check whether their patients have a psychiatric disorder.

Sleep restriction and deprivation

Daniel P Chapman (Centers for Disease Control and Prevention, Division of Adult and Community Health, Atlanta, GA, USA) presented research on sleep insufficiency in the community and the household factors that potentially impact on it; specifically, marital status and the presence of children in the household. Data from the 2002 Behavioral Risk Factor Surveillance System were presented. This ongoing, random telephone survey yielded sleep insufficiency information for 79 576 adults.

The study found that there were more reports of insufficient sleep from married women and men with children (33.9% and 26.7%, respectively) than gender-matched participants without children (21.0% of married women and 15.5% of married men). Similar results were obtained for unmarried adults: a greater proportion of unmarried women and men with children reported

insufficient sleep compared with unmarried women and men without children (35.7% vs. 26.8% and 30.6% vs. 24.9%, respectively). These data suggest that household composition impacts upon reported sleep insufficiency. Specifically, the presence of children in the household increases the likelihood of a reported sleep insufficiency, and women report more sleep insufficiency than men, particularly in households with children.

Jong-Hyun Jeong (St Vincent's Hospital, The Catholic University of Korea, Suwon, Republic of Korea) presented information from a study examining the physiological and cognitive effects of total sleep deprivation. Sixteen healthy participants remained awake under surveillance for 48 h. Several hormonal blood concentrations were measured at the beginning and end of the experiment, and reactions and vigilance tests were also performed using the Vienna Test System (Schuhfried GmbH, Mödling, Austria). The findings revealed that white blood cell counts increased significantly after sleep deprivation, as did several blood concentrations including fasting blood glucose, triiodothyronine, thyroxine, albumin, and potassium. Neurocognitive testing revealed that sleep deprivation increased reaction time and decreased correct reactions. These findings suggest that total sleep deprivation has a substantial impact on physiology in several measures as well as inducing significant cognitive impairment.

Doxepin treatment in insomnia

Howard Schwartz (Miami Research Associates, Miami, FL, USA) presented the results of a double-blind, randomized, placebo-controlled study on the use of doxepin in a model of transient insomnia. A single nighttime dose of doxepin 6 mg was given to 283 subjects and their results were compared with 282 participants who had received placebo. Participants were evaluated in a sleep lab with polysomnography and completed a morning questionnaire on various sleep measures. Subjects in the doxepin group had a 13-min improvement in latency to persistent sleep (LPS), and also had improved total sleep time, wake time after sleep, and wake after sleep onset (WASO), compared with those receiving placebo ($p<0.0001$ for all measures). Subjects receiving doxepin also had improvement in several subjective measures including subjective total sleep time. Overall, sleep architecture was preserved in the doxepin-treated patients, and adverse events were comparable between the groups. These findings suggest that, in this model of transient insomnia, doxepin 6 mg is efficacious in improving sleep quality and duration.

Alan Lankford (Sleep Disorders Center of Georgia, Atlanta, GA, USA) also presented data on the use of doxepin in insomnia. In a double-blind study, participants with ≥3 months of primary insomnia were randomized to receive placebo (n=73), doxepin 3 mg/night (n=75), or doxepin 6 mg/night (n=73) for 35 nights. All participants were evaluated with a number of polysomnography measures, including LPS and sleep efficiency (SE). The primary endpoint measured was WASO during the first night.

The study revealed that, compared with placebo, those in the doxepin groups had improved WASO scores at nights 1 and 29. SE and LPS scores for the first night were also significantly improved in the doxepin groups compared with placebo. No differences were appreciated between groups with regard to next-day residual sedation. Sleep architecture was generally preserved and the incidence of adverse events was comparable between the groups. These findings suggest that doxepin, in nightly doses of 3 or 6 mg, was efficacious in improving the symptoms of primary insomnia in adults.

Disclosures

P Ballas has no relevant financial interests to disclose.

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Sleep 2007: 21st Annual Meeting of the Associated Professional Sleep Societies

Minneapolis, MN, USA, June 9–14, 2007

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The 21st Annual Meeting of the Associated Professional Sleep Societies (APSS) was held on June 9–14 in Minneapolis, MN, USA. The meeting began with postgraduate courses on June 9–10, which covered the basics of sleep and various aspects of clinical practice, among other topics. The highly popular "Year-In-Review" course was available, as was a course on advanced polysomnography (PSG) that reviewed the much-awaited new American Academy of Sleep Medicine sleep scoring rules and provided guidance on their use. The Sleep Research Society symposia for trainees were well-attended, and provided a comprehensive introduction to sleep for aspiring sleep researchers. The scientific program held on June 11–14 consisted of invited lectures, symposia, "meet-the-professor" sessions, discussions, oral communications, poster presentations, and interest section meetings encompassing all aspects of sleep science and medicine. There were over 5000 attendees and more than 1000 abstracts were presented, reflecting the vibrancy of sleep research worldwide. The organizing committee is congratulated for assembling such a varied and stimulating program.

Mark Mahowald (Minnesota Regional Sleep Disorders Center, Minneapolis, MN, USA), who with Carlos Schenck (Minnesota Regional Sleep Disorders Center) has been a major figure in increasing our understanding of parasomnias, delivered the keynote address "Listening to a Tinkering God – Opportunities for Sleep Medicine". Key messages were that the study of patients is crucial to the identification of new avenues for sleep research, and that sleep disorders can provide insights into other neurological disorders. As an example, rapid eye movement (REM) sleep behavior disorder (RBD) occurs when muscle atonia is absent during REM sleep, resulting in patients enacting their dreams with potentially deleterious consequences. The follow-up of patients with RBD has identified an association with neurodegenerative disorders, and Parkinson's disease (PD) in particular. With RBD being a potential early harbinger of PD, its diagnosis may allow early delivery of neuroprotective agents to prevent further deterioration.

Professor Mahowald also stressed the importance of combining basic and clinical research to answer fundamental questions regarding normal and abnormal sleep physiology. The adverse effects on cognitive function of being woken from sleep (with a functional impairment equivalent to being well over the drink–drive limit) were discussed once again, emphasizing the important limitations of professional function for doctors who either work long shifts or are woken from sleep in the night. This keynote address set the scene for an interesting and educational meeting, from which a number of highlights are reported below.

Sleep deprivation and work

The importance of addressing sleep deprivation in professions responsible for medical care and public safety was highlighted by several studies from Brigham and Women's Hospital (Harvard Medical School, Boston, MA, USA). Laura Barger et al. reported on a web-based survey of 2737 physicians in their first postgraduate year who gave monthly reports of their errors and stress. Interns working five or more extended-duration shifts (≥24 h) in 1 month had significantly greater odds of reporting at least one fatigue-related significant medical error associated with an adverse patient event than those working no extended-duration shifts (odds ratio [OR] 7.0, 95% confidence interval [CI] 4.3–11). They also reported significantly more fatigue-related preventable adverse events resulting in patient death (OR 4.1, 95% CI 1.4–1.2). Clearly, given the complexities of modern clinical practice, this level of shift work has significant consequences for trainees and their patients.

In their research on the effect of sleep deprivation on visual search task success, Nayantara Santhi (Brigham and Women's Hospital) et al. studied 31 healthy volunteers in a 36-h constant routine. The volunteers underwent a visual

search task every 2 h for a target's presence in a set of simultaneously presented distractors. Accurate identification of the target was lower with sleep deprivation, especially when the target occurred less frequently. Additionally, sleep deprivation resulted in more errors. This may have important safety implications in critical low target-prevalence search tasks, for example airport baggage screeners searching for a potentially dangerous material.

In their study, Shantha Rajaratnam (Brigham and Women's Hospital) et al. screened over 4000 North American police officers for sleep disorders. Approximately 38% screened positive for a sleep disorder, with obstructive sleep apnea (OSA) being the most common by far, with a prevalence of 35.1%. The group concluded that addressing these sleep problems may improve police performance and police officer heath and safety.

Sleep duration and associated medical conditions

There is currently great interest in the associations between sleep duration and adverse health consequences such as obesity, metabolic syndrome, diabetes mellitus, and cardiovascular disease. While the relationships between sleep duration and the prevalence of these adverse consequences are "U-shaped" in adults (i.e. both short and long sleep duration are associated with adverse outcomes; see Taheri et al. for an example [1]), in children there appears to be a dose-dependent association between shorter hours of sleep and obesity [2]. A full symposium was dedicated to the population data reporting associations between sleep duration, obesity, and diabetes in children and adults. Shahrad Taheri (University of Bristol, Bristol, UK) presented preliminary data from the large ALSPAC (Avon Longitudinal Study of Parents and Children) showing that factors that may be related to short sleep duration in children are reduced time outdoors (reflecting lower physical activity) and increased television viewing. He argued that there is little to be lost in encouraging parents to provide greater opportunity for their children to have good quality sleep. This may help prevent obesity and other deleterious effects of sleep loss.

Sanjay Patel (Case Western Reserve University, Cleveland, OH, USA) presented data from the Nurses' Health Study showing a longitudinal association between short sleep duration and the development of obesity. In this major study, no association between sleep duration and self-reported increased food intake or reduced physical activity was seen [3], but Dr Patel acknowledged the shortcomings of self-reporting on these measures. In his presentation, Daniel Gottlieb (Boston University, Boston, MA, USA) described the complexities of the associations between sleep duration and diabetes.

A major discussion point at the conference was the aforementioned U-shaped relationship between sleep duration and the adverse outcomes of diabetes and obesity in adults, such that the coverage in this symposium was complemented by oral and poster communications confirming the associations – now supplemented with a relationship between short sleep duration and the metabolic syndrome.

Diane Lauderdale (University of Chicago, Chicago, IL, USA) et al. reported findings from an investigation ancillary to the CARDIA (Coronary Artery Risk Development In Young Adults) study. Wrist actigraphy was carried out for two 3-day periods approximately 1 year apart in 669 participants aged between 38 and 50 years, in addition to measurements of body weight, fasting glucose level, fasting insulin level, and insulin sensitivity. Sleep duration was significantly associated with changes in fasting insulin level ($p=0.02$) and insulin sensitivity (derived from homeostatic model assessment; $p=0.01$). Again, a U-shaped association was observed, i.e. both short and long sleep durations were associated with reduced insulin sensitivity. Mean change in body mass index (BMI) was greatest in shortest sleepers, but this association was not statistically significant.

Hiromi Nakajima (Nihon University, Tokyo, Japan) et al. reported on the potential associations of glycated hemoglobin and fasting plasma glucose with sleep duration in a rural community in the Japanese Tohoku provinces. The participants were 406 men and 656 women aged ≥20 years. The researchers found that both short and long self-reported sleep durations were associated with an increased prevalence of high glycated hemoglobin (i.e. hyperglycemia).

Katie Stone (California Pacific Medical Center, San Francisco, CA, USA) et al. studied the relationship between sleep duration (measured using actigraphy) and obesity in over 6000 older individuals enrolled in the Study of Osteoporotic Fractures (3052 women; mean age 84 years) or the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) study (3058 men; mean age 76 years). Sleep-disordered breathing (SDB) in men (measured using the apnea–hypopnea index [AHI]) was investigated using in-home overnight PSG. The group found that older men with total sleep time (TST) <5 h had an increased risk of obesity (defined as BMI ≥30 kg/m^2) compared with those with TST ≥7 to <8 h (OR 3.7, 95% CI 2.7–5.0). These findings were consistent, but less striking, in older women (OR 2.3, 95% CI 1.6–3.1). Similar findings were observed regarding the relationship between sleep duration and waist circumference. Among men, the relationship between TST and obesity was independent of the AHI.

Martica Hall (University of Pittsburgh, Pittsburgh, PA, USA) et al. reported on their study of 334 multi-ethnic mid-life women (mean age 51 years; 85% were perimenopausal)

who underwent 3-night in-home PSG and assessment using the Pittsburgh Sleep Quality Index. AHI was found to be significantly higher in women with the metabolic syndrome than in those without (10.53 compared with 7.05; $p<0.01$). It was also observed that the greater the number of sleep problems, the greater the chance of a person having the metabolic syndrome.

Jacques Montplaisir (University of Montreal, Montreal, QC, Canada) discussed a study of over 1100 Canadian children whose parents reported annually on their sleep duration from the age of 2.5 to 6 years. BMI was measured at the age of 6 years. Four sleep patterns were identified in children followed longitudinally: a short, persistent pattern (6.0%) where children slept <10 hours per night until the age of 6 years; a 10-hour, persistent pattern (50.3%); an 11-h, persistent pattern (38.9%); and a short, increasing pattern (4.8%), where children slept fewer hours in early childhood but increased their sleep duration later. A significant difference in the distribution of BMI as a function of sleep duration pattern was noted ($p<0.001$). Compared with 11-hour persistent sleepers, the OR of being overweight was almost three-fold higher for both short, persistent sleepers and short, increasing sleepers ($p=0.01$).

Obesity and the metabolic syndrome are particularly prevalent in individuals of black and Hispanic origin and in those in low socioeconomic groups (see, for example, Mensah et al. [4]). Lauren Hale (State University of New York at Stony Brook, Stony Brook, NY, USA) and D Phuong Do (University of Michigan, Ann Arbor, MI, USA) studied a 1990 sub-sample of the National Health Interview Survey (n=32 184) and found that black respondents had an increased risk of being short and long sleepers relative to white respondents (OR 1.66; $p<0.001$ and OR 1.42; $p<0.05$). Subjects of Hispanic origin were more likely to have short sleep duration relative to white respondents (OR 1.27; $p<0.01$). The investigators also found that living in an inner city was associated with an increased risk of short sleeping relative to living in non-urban areas, and concluded that their results are in agreement with the hypothesis that ethnic differences in health may be contributed to by unhealthy sleeping patterns.

Continuing the theme of sleep duration and adverse health outcomes, Yoshitaka Kaneita (Nihon University) reported data from the National Health and Nutrition Survey of Japan showing that, among women, both short and long sleep durations were associated with an increased prevalence of atherogenic dyslipidemia (in this case, high triglyceride levels and low high-density lipoprotein cholesterol levels). No such associations were observed in men.

A reduction in heart rate variability (HRV; beat-to-beat changes in heart rate) has been associated with increased cardiovascular risk. Siobhan Banks (University of Pennsylvania School of Medicine, Philadelphia, PA, USA) et al. studied HRV after 5 nights of sleep restriction (time in bed of 4 h) in 39 participants. Sleep restriction resulted in statistically significantly reduced HRV ($p=0.05$), perhaps suggesting a pathway linking short sleep duration with increased cardiovascular disease and mortality. HRV was also investigated by Phyllis Stein (Washington University in St. Louis, Saint Louis, MO, USA) et al. They investigated HRV as determined from overnight PSG in a sub-sample from the Sleep Heart Health Study (n=272; average age 76±4 years) and found a significant association between increased 5-year mortality and decreased HRV.

Xianchen Liu and Daniel Buysse (University of Pittsburgh) carried out an interesting questionnaire survey of 1362 adolescents in five high schools in China. They found that sleeping <8 h at night, frequent nightmares, and difficulty initiating sleep were significantly associated with the likelihood of drinking alcohol, after adjustment for potential confounders (ORs 1.6, 1.6, and 1.5, respectively). It is well known that alcohol has deleterious consequences on sleep, and cross-sectional studies such as this one have pointed to a relationship between short sleep duration and alcohol and substance use in adolescents. Prospective studies are now necessary to determine the cause–effect relationship.

Legal aspects of RBD and sleepwalking

An interesting workshop took place discussing the medico-legal aspects of sleepwalking and RBD. The discussions confirmed that overnight sleep studies may not be helpful for determining whether an individual is a sleepwalker; instead they may be more helpful for diagnosing RBD. There were also interesting data presented on homicides where sleepwalking was claimed in the defense cases. Where alcohol is involved, it was felt that the strength of the defense case could be greatly diminished.

Normal sleep in childhood

There were several presentations providing normative sleep data in childhood. Good quality normative data is essential for giving accurate advice regarding childhood sleep problems. Anuj Chawla (Tulane University, New Orleans, LA, USA) et al. reported on the impact of socioeconomic status on children's sleep. Parents bringing their child (n=64) for an acute illness or routine appointment filled out the 35-item Children's Sleep Habits Questionnaire [5]. The investigators found that children from lower socioeconomic groups (assessed using the Hollingshead score) had worse sleeping patterns. The relationship between socioeconomic status and sleep has been explored by several, mainly cross-sectional studies in children and adolescents (see, for

example, Acebo et al. [6]), with conflicting results. Further information from a large longitudinal study may shed light on this relationship.

Dr Taheri et al. also examined factors associated with sleep duration in infants aged 6–8 months from the large ALSPAC study. An interesting finding was that firstborn infants were found to sleep less, both during the day and at night. Compared with those from higher socioeconomic groups, children from lower socioeconomic groups tended to sleep for a shorter time at night (4 min; $p<0.02$), but for slightly longer during the day (8 min; $p=0.001$). Interestingly, children with obese mothers tended to sleep less at night.

Insomnia and circadian sleep disorders

Workshops at the event highlighted the impact of insomnia in the home, workplace, and community. Cognitive–behavioral therapy (CBT) for insomnia is regarded by many as the treatment of choice for long-term success, but great debate was generated regarding who should carry it out and in which clinical setting. It was felt that there is a pressing need for more personnel, especially clinical psychologists, to be available to help support professionals in implementing the therapy.

Two studies from Northwestern University (Chicago, IL, USA) provided interesting new results on insomnia and circadian sleep disorders. Erik Naylor et al. provided preliminary data suggesting that, compared with sleep hygiene advice alone, aerobic exercise in combination with sleep hygiene advice improves subjective sleep quality in sedentary older individuals with chronic insomnia. Meanwhile, Ashley Jaksa et al. studied psychiatric co-morbidities in 30 patients with delayed sleep phase syndrome (DSPS; mean age 34±11.4 years). Mood, anxiety, and substance abuse disorders were found to be common, with one or more of these conditions present in around half of the DSPS patients.

Jonathan Emens (Oregon Health and Science University, Portland, OR, USA) et al. studied phase angle of entrainment (defined as the interval of time, or phase-angle difference [PAD], between dim-light melatonin onset (DLMO) and mid-sleep; a measure of the alignment of sleep–wake schedule with the external light–dark cycle) in 53 healthy adults recruited to a diurnal preference study. The investigators found that mean PAD was 40 min longer in women compared with men (7.18±0.99 h vs. 6.52±1.27 h). The group concluded that this finding has implications for diagnosis and treatment of circadian rhythm sleep disorders.

Sleep in psychiatric disorders

Mariana Szklo-Coxe (University of Wisconsin-Madison, Madison, WI, USA) et al. presented data on the association between insomnia and depression in 595 participants from the Wisconsin Sleep Cohort Study. In agreement with previous epidemiological studies (e.g. Breslau et al. [7]), the investigators found that insomnia strongly predicted for depression.

Continuing the discussion on sleep disorders and mental illness, Rebecca Bernert (Florida State University, Tallahassee, FL, USA) et al. presented data on 14 456 community-based older individuals over a 10-year period in a longitudinal, multi-site cohort study: EPESE (Established Populations for Epidemiological Studies of the Elderly). The group found that poor self-reported sleep at baseline (measured with a 5-item sleep quality scale) predicted eventual death by suicide, even after controlling for the influence of depression ($p<0.001$).

Sleep-disordered breathing

Pediatric sleep physicians stressed the importance of assessing SDB in children who snore, particularly those who have been referred for tonsillectomy and adenoidectomy. Sleep studies should be performed to determine the presence and severity of sleep apnea in this population. In adults, there was much debate regarding the role of portable monitoring equipment (multi-channel devices that measure airflow and chest and abdominal movements, and include oximetry, with or without electroencephalography) in the diagnosis of SDB. The overall view was that this equipment may well have a role, but concerns were raised that those providing a portable sleep study service should have appropriate training and accreditation, and that there must be some evidence of quality control. Certainly, as waiting lists for in-house PSG continue to rise, portable monitoring use may become more common.

There was further recognition that some patients with OSA, once established on continuous positive airway pressure therapy, may develop central apnea events. The management strategy for this "complex sleep apnea" is unclear, but there is great interest in the use of adaptive servo-ventilation.

SDB in children and adolescents

Hawley Montgomery-Downs (West Virginia University, Morgantown, WV, USA) and David Gozal (University of Louisville, Louisville, KY, USA) presented preliminary data regarding the mode of infant feeding and development of OSA. They surveyed the parents of children undergoing sleep studies (n=197; mean age 6.7±2.9 years) to elicit whether each child had been breast- or formula-fed, or a combination of both, as an infant. Given the known health benefits of breastfeeding, only a disappointing 10% of the children included had been exclusively breastfed. Children who had been breastfed for ≥2 months had a range of benefits compared with those who had not, including lower AHI ($p=0.053$), lower snore arousal index ($p=0.010$), and lower respiratory arousal index ($p=0.027$). Whether breastfeeding

does indeed protect against SDB requires a larger, non-selected population study.

Dr Montgomery-Downs also reported on the potentially heightened risk for SDB among infants and toddlers born prematurely, highlighting the possible importance of the condition as a contributory factor in the impaired cognitive function of this population. This opens the possibility of routine SDB screening as a means of preventing some of the persisting post-neonatal developmental disadvantage for such children.

Several teams reported the results of studies on sleep position and OSA in children. In theirs, Nisha Rathi (University of Texas Health Science Center at Houston, Houston, TX, USA) et al. found no significant association between sleep position and OSA in infants aged 8–12 months, although the group did note that REM sleep was linked with worse OSA than non-REM sleep ($p=0.015$). Russell Gibson (University of Michigan) et al. showed that the severity of SDB (as measured using the AHI) was greater in the supine than the non-supine sleeping position for children aged >6 years, resembling findings in adults. In children under this age, however, there was no such effect.

An association in mid-childhood between the occurrence of habitual snoring and enuresis was reported by Oscar Sans Capdevila (University of Louisville) et al. (OR 2.79, CI 2.50–3.13; $p<0.00001$). However, the group did not observe a similar correlation between the severity of habitual snoring and enuresis prevalence.

Christine Won and Christian Guilleminault (Stanford University, Stanford, CA, USA) reviewed the PSG data of 1079 pre-pubertal children and adolescents referred to the Stanford Sleep Disorders Center. They found no differences between males and females in terms of age, BMI, AHI, or sleep stages among pre-pubertal children with or without OSA, and among adolescents without OSA. However, among adolescents with OSA, boys exhibited a significantly lower TST than girls (388±81 min vs. 419±78 min). Valerie Crabtree (University of Louisville) et al. reported on a study of 785 children from the community aged 5–8 years who underwent nocturnal PSG and neurocognitive assessment (for example, Clinical Evaluation of Language Fundamentals and the Peabody Picture Vocabulary Test II). Measures of SDB such as high AHI, sleep pressure score, and obstructive apnea index were found to be significantly related to almost all assessed areas of neurocognitive function. Lastly, Joseph Crisalli (Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA) et al. reported a study suggesting that home overnight oximetry is useful in screening overweight or obese children referred to sleep centers. Given the increased prevalence of obesity, this screening may allow PSG to be prioritized.

Narcolepsy and the hypocretin (orexin) system

Human leukocyte antigen (HLA)-positive narcolepsy–cataplexy is associated with deficient hypocretin (orexin) neurotransmission. Hypocretin neurons are located in the lateral and posterior hypothalamus. It is believed that narcolepsy–cataplexy occurs after destruction of hypocretin neurons by an unknown process that could possibly involve autoimmunity, given the tight HLA association. The majority of patients with narcolepsy–cataplexy have undetectable hypocretin levels in their cerebrospinal fluid (CSF). Makoto Honda (Center for Narcolepsy, Stanford, and Tokyo Institute of Psychiatry, Tokyo, Japan) et al. reported on their DNA microarray study of narcolepsy brains. Eight control and six narcolepsy *post mortem*, human posterior hypothalamic samples were used. As expected, the most down-regulated gene in narcolepsy hypothalami was that encoding hypocretin. The gene for an insulin-like growth factor binding protein (IGFBP-3), which was found to be highly expressed in hypocretin neurons, was also down-regulated. The potential role of this novel, candidate narcolepsy-related gene in the pathogenesis of the condition remains to be determined.

Jamie Zeitzer (Stanford University) et al. reported that although lumbar CSF concentrations of hypocretin were in the normal range in patients with Alzheimer's disease, they were inversely correlated with fragmentation of daytime wakefulness (i.e. the number of daily naps; $p<0.05$). The range of variation in CSF hypocretin levels may, therefore, be associated with various abnormalities in the maintenance of wakefulness.

Hypocretin neurons may also be vulnerable in other neurodegenerative disorders. Thomas Thannickal (University of California, Los Angeles, North Hills, CA, USA) et al. studied the *post mortem* brains of 11 patients with PD and five healthy controls. There was a significant correlation between the loss of hypocretin and adjacent neurons (melanin-concentrating hormone neurons) in the hypothalamus and the clinical stage of PD. The authors concluded that therapies proven to be effective in narcolepsy may also be useful in treating the narcolepsy-like symptoms of PD.

An association between narcolepsy, obesity, and type 2 diabetes has been previously reported (for example, by Honda et al [8]). Aliuddin Khaja (Center for Narcolepsy, Stanford University) et al. reported an investigation of possible sex differences in the BMI distribution of 168 patients with narcolepsy and hypocretin deficiency (in CSF). They found that, compared with male patients, the risk of obesity was higher in females (OR 2.4; $p=0.02$).

Cataplexy is commonly triggered by emotional stimuli, in particular laughter. Sophie Schwartz (University of Geneva, Geneva, Switzerland) et al. carried out a functional magnetic

resonance imaging study to investigate the regional brain responses to humorous stimuli in healthy volunteers and drug-free patients with narcolepsy and cataplexy. They found that, while the same brain circuitry was used to respond to humorous stimuli in those with narcolepsy and control volunteers, narcolepsy patients showed comparatively reduced hypothalamic, but enhanced amygdalic, response to these stimuli.

Academic sleep centers and the future of sleep medicine

There was great enthusiasm at the meeting for developing and promoting academic sleep centers, which were also highlighted in a recent report on sleep disorders and sleep deprivation from the Institute of Medicine in the US [9]. Allan Pack (University of Pennsylvania, Philadelphia, PA, USA) pleaded with all delegates to continue their valuable research work and to raise the profile of sleep medicine, making it more academic and more challenging. It is certain that more will be heard on this subject at next year's meeting of the APSS in Baltimore (MD, USA).

Disclosures

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