REMEDICA

VOLUME 1 NUMBER 3 2008

The International Journal of

SLEEP AND WAKEFULNESS

PRIMARY CARE EDITION

Effects of Smoking Cessation and Related Treatments on Sleep
Ian M Colrain and Gary E Swan

Sleep-Disordered Breathing in Pregnancy
Bilgay Izci Balserak

Conceptualizations of Sleepiness and the Measurement of Hypersomnia
Meeta Singh

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This journal is supported by an educational grant from Cephalon.

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

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Birgit Wiswe, MD: No relevant financial relationships to disclose.

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

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 The International Journal of Sleep and Wakefulness – Primary Care (1754-3088) is published four times a year. Additional subscription information is available from the publisher.

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Tel: +44 (0)20 7759 2999 Fax: +44 (0)20 7759 2951
Email: info@remedica.com

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1754-3088

Contents

LEADING ARTICLE

Effects of Smoking Cessation and Related Treatments on Sleep

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Nicotine, the substance in tobacco primarily responsible for dependence, has a major stimulant effect. However, it also impacts upon a number of neurotransmitter systems known to be involved in the regulation of sleep and wakefulness. Pharmacotherapy for smoking cessation involves the administration of nicotine (nicotine replacement therapies), bupropion (a drug thought to affect the dopamine, norepinephrine, and serotonin systems), varenicline (a partial nicotinic acetylcholine receptor agonist), or combinations of these. Therefore, it is reasonable to hypothesize that both withdrawal from nicotine when quitting smoking, and therapies used to assist with this task, could lead to sleep disturbances. The evaluation of these hypotheses is potentially important for gaining an understanding of why failure to quit is prevalent, and why these pharmacotherapies have low efficacy for long-term abstinence. This article reviews the available literature, investigating the effect of smoking cessation, and of pharmacotherapy used for smoking cessation, on subjective and objective measures of sleep disturbance. *Int J Sleep Wakefulness – Prim Care* 2007;**1**(3):90–4.

Smoking is a major health problem with direct causal impact on elevated cardiovascular, cerebrovascular, and respiratory morbidity and mortality rates. Substantial evidence suggests that nicotine plays a pivotal role in mediating the addictive nature of smoking in humans [1]. While there is significant individual variability, the half-life of nicotine in the brain is approximately 2 h and, depending on the frequency of smoking, the drug has the potential to accumulate throughout the day and persist into the sleep period [2]. As nicotine has effects on several neurotransmitter systems known to be involved in the regulation of sleep and wakefulness, this accumulation and persistence has the potential to affect sleep. In addition to its direct agonist effect on nicotinic cholinergic post-synaptic receptors, nicotine facilitates the presynaptic release of dopamine, norepinephrine, serotonin, glutamate, and γ-aminobutyric acid [3], and, with continued use, tolerance to the acute effects of nicotine develops [4].

Smoking cessation and sleep disruption

Smoking cessation and its associated nicotine withdrawal leads to a disruption of the neurochemistry in the central and autonomic nervous systems and, as with withdrawal from many other neuroactive addictive substances, appears to have an acute disruptive effect on sleep, a factor that may be implicated in the relapse of susceptible individuals [5].

Sleep disturbance is commonly self-reported by quitting smokers as a prominent symptom [6] that persists for several weeks post-cessation [7]. Sleep diary ratings or questionnaires have tended to show an increase in the perceived number of awakenings following quitting [8–10]. In a recent study, Shiffman et al. used a digital personal assistant to question participants several times daily for 1 week before and ≤3 weeks after quitting [11]. Upon awakening in the morning, several questions were asked relating to trouble falling asleep the previous evening, frequency of awakenings, and ratings of sleep quality. The investigators observed that the individuals' sleep was disturbed for around 1 week after giving up; baseline levels of all symptoms were reached within 10 days of smoking cessation [11].

Only a small number of sleep-laboratory studies carried out to assess the impact of smoking cessation on objective measures of sleep are evident in the literature [12–16]. The investigators of these studies primarily used the Rechtschaffen and Kales scoring criteria, which require a period of electroencephalogram (EEG) arousal to last ≥15 s in order to be recognized as an interruption of sleep [17].

Soldatos et al. studied eight male smokers for three consecutive nights prior to quitting and for five consecutive nights post-cessation [12]. There were no differences in the global measures of time awake after sleep onset and the percentage of time spent in each sleep stage. However,

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sleep onset latency decreased following smoking cessation. While the data are difficult to interpret, the investigators suggested that sleep quality improved following smoking cessation [12]. Another equally plausible hypothesis is that initial sleep fragmentation leads to daytime sleepiness and a reduction in sleep onset latency. Unfortunately, as the frequency of arousals from sleep was not reported, it is not possible to draw a firm conclusion.

In their study, Prosise et al. studied 10 men and eight women and found that the number of awakenings increased significantly between the pre- and post-cessation periods [13]. Furthermore, Multiple Sleep Latency Test data collected each day following nightly sleep studies indicated a significant decrease in sleep onset latency upon cessation, suggestive of an increased level of sleepiness [13].

Wetter et al. examined the sleep of 34 quitting smokers, where half of the group used 24-h, 22-mg nicotine replacement therapy (NRT) patches and the other half used placebo patches [14]. Smokers were evaluated using standard polysomnography on five occasions: seven and five nights before quitting, and on post-cessation nights one, three, and five. Both the NRT and placebo groups experienced an increased number of arousals on the first post-cessation night, with the control group continuing to have more arousals on nights three and five compared with baseline values [14].

In a second article, Wetter et al. reported secondary analyses of their original dataset, considering additional variables including gender differences [15]. Men in both the placebo and NRT groups displayed an increased number of awakenings per hour during the first post-cessation night, compared with baseline values. This pattern was maintained in the male placebo group for the third and fifth post-cessation nights. In contrast, women had fewer awakenings overall (including at baseline), but both the placebo and NRT groups displayed an increase in the number of awakenings per hour during the third post-cessation night [15].

In a third article, Wetter et al. studied a new sample of 13 women, some of whom had a history of depression [16]. Smoking cessation was accomplished with counseling support but without pharmacological intervention. Measures relating to the timing of rapid eye movement (REM) sleep were the only variables that differentiated the depressed patients from the healthy controls. Women in both groups showed increases in the number of awakenings and sleep-stage shifts, the amount of time spent awake after sleep onset, and the percentage of stage-one sleep on the third post-cessation night. This was accompanied by a decrease in the percentage of slow-wave sleep on the same night [16].

In addition to these studies, the present authors recently presented preliminary data from an ongoing study examining the impact of smoking cessation on central and autonomic nervous systems during sleep [18]. Data from 24 smokers (11 women) recorded on a baseline night (while still smoking) were compared with those from the first night after cessation. Sleep efficiency was decreased from 87.8% on the baseline night to 83.7% on the night of cessation ($p<0.05$), due to statistically significant increases in both the amount of time awake after sleep onset (from 34.8 min to 61.2 min; $p<0.001$) and the number of wake periods (from 15.6 to 21.4; $p<0.01$) as defined using the criteria of Rechtschaffen and Kales [17].

Pharmacological treatments for smoking cessation and sleep disruption

Pharmacological treatments designed to assist with smoking cessation are ineffective for sustained abstinence in many smokers [4]. Preliminary evidence suggests that the administration of NRT, bupropion, or both can result in disrupted sleep, particularly in women [16], and this may be one reason for the failure of these treatments to yield sustained abstinence. Varenicline, the most recently adopted treatment, has not yet been sufficiently studied to draw conclusions with regards to its impact on sleep.

NRT

Reviews of results from the small number of studies examining the relationship between NRT and sleep highlight the prominence of sleep disturbance [19]. Most studies in this area have included one or two self-report questions to determine the presence of side effects, and have used protocols that involved participants wearing a transdermal nicotine patch overnight. This approach yielded higher rates of sleep disturbance with NRT than with placebo [20], with transdermal nicotine users reporting sleep disturbance three times more often than recipients of placebo patches [21]. Additionally, difficulty sleeping has been reported in uncontrolled NRT studies [22,23].

In a laboratory setting, Gillin et al. investigated sleep following the use of 7-mg or 14-mg nicotine patches or placebo by non-smokers [24]. The investigators observed a dose-dependent effect of nicotine on the number of early morning awakenings and reductions in REM sleep [24]. Davila et al. also used low-dose transdermal nicotine in non-smokers, and reported a decrease in the number of sleep-related breathing events but no impact on sleep itself [25]. In a study of 7-mg, 14-mg, and 21-mg patches, the Transdermal Nicotine Study Group found a dose–response relationship between nicotine and self-reported insomnia in non-smokers [26].

In their recent study, Page et al. sought to assess the impact of NRT on dream content in 15 smokers [27]. A 21-mg or a

14-mg patch was applied by participants, depending on the number of cigarettes typically smoked per day. The subjects abstained from smoking for only 2 h prior to bedtime, and spent two nights in the sleep laboratory, one wearing an active patch and the other in a placebo condition. Subjects were woken during periods of REM and stage-two sleep in order to assess sleep-related cognitive activity immediately prior to waking. The investigators reported a significant decrease in the percentage of sleep time spent in REM sleep while receiving active NRT compared with placebo. Furthermore, they noted an increase in the percentage of time spent awake (16.8±9.2% vs. 31.6±19.4%) and in the average number of microarousals per hour (15.4±5.2 vs. 19.5±7.5) when the active patches were worn compared with placebo, but did not comment on the level of statistical significance [27].

Upon comparing active and placebo patches in male and female smokers who were attempting to quit, Wetter et al. [14] noted few differences when sleep was scored using Rechtschaffen's and Kales' criteria (that is, ignoring brief but clinically significant arousals) [17]. However, there was evidence indicating that NRT could be particularly problematic for sleep quality in women. In the second article from this group, data from men and women were analyzed separately, and, as described above, it was found that the recovery from the deterioration in sleep quality observed following the first night of cessation in all groups was not present in women using active NRT [15]. These women also showed a further deterioration on the fifth post-cessation night [15]. The authors pointed to this finding as an indication of a possible iatrogenic effect of NRT on sleep in women. This hypothesis is supported by questionnaire data from Gourlay et al. who observed sleep problems in 48.1% of participants in a trial of NRT, and found that female gender was a significant predictor of sleep disturbance being reported as an adverse event [28].

Most recently, in an open-label, crossover study, 20 smokers (nine women) wore 21-mg or 14-mg nicotine patches for 24 h or 16 h, respectively [29,30]. The effect of these patches on sleep was measured on the second night of a period of smoking abstinence and compared with baseline sleep recorded the preceding night, following one day of abstinence without treatment. Gender differences were not evaluated. Aubin et al. reported that, compared with the preceding night's sleep, slow-wave sleep increased when the 24-h patch was used, and decreased when the 16-h patch was used [29]. However, this result may be due to an unusually high level of slow-wave sleep on the night prior to the 16-h patch condition, as the "increase" in the percentage of the night spent in slow-wave sleep with the 24-h patch was small and extremely variable (1.86±8.63%).

Staner et al. reported a re-analysis of the same data [30]. In addition to the effect on slow-wave sleep, the authors reported a greater baseline-to-treatment decrease in microarousals and a greater increase in the density of eye movements and high-frequency EEG power during REM sleep in the 24-h patch condition, compared with use of the 16-h patch [30]. These results probably reflect the action of the available nicotine on the cholinergic systems that are active in REM sleep. The data are difficult to compare with previously published results as treatment began on the second post-cessation night.

Bupropion

There are no published systematic study results relating to the direct effect of bupropion on sleep. However, clinical trials of bupropion as a smoking cessation treatment have noted its adverse impact on subjective ratings of sleep quality [31,32]. This effect was confirmed in an extensive review of published research findings and unpublished study results from the pharmaceutical industry [33].

In the context of its use as an antidepressant, objective laboratory investigations of the effect of bupropion on sleep indicated that it has a negative impact on sleep continuity [34]. Unlike many other antidepressants, bupropion does not appear to have REM sleep-suppressant effects [35,36], and it may even increase the proportion, and decrease the latency, of REM sleep [37]. There is at least one report of clinical effectiveness being associated with increased REM latency [38]; however, this was in a depressed patient who also had narcolepsy.

Additional studies examining the efficacy of bupropion for smoking cessation have highlighted its impact on subjectively rated sleep. In a dose–response trial performed by Hurt et al., insomnia was a prominent side effect for 21% of patients receiving a placebo [39]. The insomnia rate increased to 29% for patients treated with bupropion at a dose of 150 mg/day, and rose further, to 35%, for patients who received 300 mg/day [39]. In a comparative trial with NRT, insomnia was present in 42% of patients treated with bupropion 300 mg/day, 30% of patients using transdermal nicotine at an initial dose of 21 mg/day (which was then reduced sequentially to 14 mg/day and 7 mg/day), and 48% of patients taking combination bupropion–transdermal nicotine treatment [40]. In comparison, the incidence of insomnia in the placebo group was 20%, which was similar to that reported in the study by Hurt et al. [39].

In a double-blind, placebo-controlled trial of bupropion, Paul et al. found that significantly more awakenings and more difficulty returning to sleep were reported on a side-effects questionnaire by those taking the active drug compared with those receiving placebo [41]. In the first

Table 1. The percentages of patients reporting insomnia as an adverse event in clinical trials of varenicline (and bupropion when compared with varenicline). Note the variability within the Tonstad et al. study results [51] depending on whether varenicline was given blinded or open-label.

Study	Treatment		
	Placebo	Varenicline 1 mg twice daily	Bupropion 300 mg daily
Gonzales et al. [48]	12.8%	14.0%	21.9%
Jorenby et al. [47]	12.4%	14.3%	21.2%
Nides et al. [50]	22%	35.5%	45.2%
Oncken et al. [49]	11.6%	37.2%	–
Tonstad et al. [51]:			
open-label phase	–	19.6%	–
blinded phase	2.8%	2.7%	–
Tsai et al. [53]	13.7%	15.1%	–
Williams et al. [52]	9.5%	19.1%	–

"actual-practice" trial of slow-release bupropion, Swan et al. also found that a significantly higher proportion of the participants who were receiving 300 mg/day reported insomnia, compared with those taking 150 mg/day [42]. Lastly, in a comparison of bupropion therapy, NRT, and a no-treatment control group, sleep disturbance was reported as a side effect in 40%, 38%, and 9.6% of the respective participant groups [43].

Combined therapy using bupropion and transdermal nicotine is now being recommended as an optional treatment for smoking cessation in recalcitrant smokers [44]. The proportion of smokers still abstinent at 12 months has been reported to be 35.5% with combined therapy versus 16.4% with transdermal nicotine alone, and 30.3% with bupropion alone [40]. These values are likely to be inflated due to the use of motivated volunteers and the constant monitoring for relapse. Nevertheless, even with the best treatment under optimal conditions, almost two-thirds of participants relapsed. The most prominent side effect reported in this study was insomnia, which occurred in almost half of the combination therapy sample (47.5% of patients) [40].

There is one documented case of a bupropion-induced parasomnia. Khazaal et al. reported somnambulism in a 33-year-old man, which commenced 2 days post-cessation, and 16 days after starting bupropion therapy [45]. There were several episodes of sleepwalking and sleep-eating over a 2-week period, all associated with amnesia [45].

Varenicline

Varenicline is a partial agonist selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor [46]. It has been approved by the US Food and Drug Administration for use in smoking cessation, and preliminary results have shown it to confer higher efficacy than unassisted cessation attempts and bupropion therapy [47,48]. There have been no laboratory or questionnaire studies to address the effect of varenicline on sleep. However, incidental data are available from adverse events reported in clinical trials (Table 1) [47–53]. These show extremely variable results with the incidence of insomnia ranging from 2.7% to 37% (2.8% to 22% for those receiving placebo). In one investigation, the incidence of insomnia with varenicline treatment was 2.7% in a blinded phase and 19.6% in an open-label period [51]. In the three studies that compared the effects of varenicline with those of bupropion, the rate of insomnia was greater in the group taking bupropion [47,48,50]. Several studies reported vivid dreaming or an increased amount of dreaming as an adverse event; again, reported rates were highly variable, ranging from 1% [51] to 22.7% [52].

Clearly, the measured probability of an adverse event is highly dependent on the questions that are asked, in addition to how and when they are presented to study participants. In a recent study that examined the side effects of varenicline in 746 smokers, difficulty sleeping was reported by 42% of participants and abnormal dreams by 56% when questioned after 28 days of use [54]. Women were significantly more likely than men to report difficulty sleeping as a side effect [54].

It is possible that as more research is conducted outside of the randomized, double-blind, placebo-controlled clinical trial environment, the observed prevalence of sleep complaints will increase. There is also a need for laboratory-based observations to assess both the direct effects of varenicline on sleep, and the impact of these effects on daytime functioning.

Conclusions

Smoking cessation, NRT, and other pharmacotherapies used to assist with smoking cessation are all clearly linked with sleep disturbance as an adverse event in clinical trials. NRT and bupropion are associated with subjective reports of sleep disturbance, and there is limited evidence of objectively observed sleep disruption in laboratory studies of NRT. It is likely that this sleep disruption is a factor in subsequent relapse, as it will lead to daytime sleepiness and dysphoric mood symptoms. Proactive counseling to inform quitting smokers of likely sleep problems, along with the provision of suggestions or treatment for the management of these problems may assist with smoking cessation.

Disclosures

The authors have no relevant financial relationships to disclose.

Acknowledgment

The preparation of this article was supported by grant DA016427 from the National Institute on Drug Abuse (Bethesda, MD, USA).

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Sleep-Disordered Breathing in Pregnancy

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LEADING ARTICLE

Manifestations of sleep-disordered breathing (SDB) include snoring, upper-airway flow limitation, and obstructive sleep apnea. These are common in pregnancy, particularly during the third trimester. Hormonal and biochemical changes, and the physical effect of the enlarging uterus during pregnancy, cause physiological and anatomical changes in the respiratory system. While some of these pregnancy-related changes reduce the risk of SDB, others can increase its incidence and severity, which may in turn be associated with maternal and fetal complications during pregnancy. This article reviews SDB in pregnancy, the associated complications, and related practical implications. It also highlights the key study results in these areas. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(3):95–105.

General changes in sleep architecture and sleep quality in pregnancy and *post partum*

Sleep fragmentations and alterations are reported by the majority of women during pregnancy [1–15]. As such, a "pregnancy-associated sleep disorder" is identified in the *International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual* as a distinct clinical disorder, characterized by the occurrence of either insomnia or excessive sleepiness during pregnancy [5].

In the first trimester of pregnancy, nocturnal awakenings (which are associated with nausea and vomiting), total sleep time (TST), and daytime sleepiness increase. Overall sleep quality and the percentage of slow-wave sleep (SWS) decrease significantly in comparison with the pre-pregnancy period [4–7].

Sleep is more normal in the second trimester, when the percentage of SWS increases compared with that in the first trimester [5,8–10]. However, at the end of the second trimester (after 23–24 weeks of gestation), TST falls [4] and sleep complaints and the frequency of restless sleep increase [7].

In the third trimester, insomnia, nocturnal awakenings, unrefreshing sleep, increased daytime sleepiness, and impaired daytime alertness are reported [5,8–14]. Furthermore, more time is spent in sleep stages one or two, sleep stages three and four have been observed to shorten, and sleep efficiency decreases compared with non-pregnant women [4,9,10,12–15]. Study results indicate that daytime sleepiness is increased in up to 65% of pregnant women by the end of pregnancy, due to sleep disturbances [1,3]. Reasons for such disturbances in the third trimester include [1–3,5–8,10,12,15,16]:

- Urinary frequency.
- Backache.
- Fetal movement.
- Uterine activity.
- General abdominal discomfort.
- Leg cramps.
- Restless legs syndrome.
- Heartburn.
- Shortness of breath.

Frequent awakenings may cause respiratory instability, such as periodic breathing during sleep onset, and increase the risk and frequency of sleep-disordered breathing (SDB) events [17].

In the first month following delivery, the degree of maternal sleep disturbances increases considerably [4,9]. Rapid eye movement (REM) sleep decreases and then normalizes after 2 weeks, and stage four sleep returns to pre-pregnancy levels [5,18]. An increased concentration of circulating prolactin has been found to increase SWS in women who are breastfeeding [19]. However, TST and sleep efficiency remain low for up to 3 months [4,6,14], probably due to the need to feed the baby, the infant's circadian rhythm, and hormonal changes [4,12].

Manifestations of SDB in pregnancy

SDB refers to the entire spectrum of breathing disorders during sleep. The physiological spectrum of SDB may range from partial airway collapse to increased upper-airway (UA) resistance (experienced as loud snoring and episodes of hypopnea), to complete airway collapse (resulting in breath-

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ing pauses lasting for 60 s or more) [20]. The mildest form of SDB is intermittent snoring without episodes of apnea or hypoventilation, and the most severe form of SDB is arguably the obesity–hypoventilation syndrome [21].

Snoring

The results of numerous studies have shown that both the severity and frequency of snoring increase steadily during pregnancy [1,3,22–25]. Self-reported habitual snoring has been observed to increase by up to 46% in healthy pregnant women, and by up to 59% in preeclamptic women, during the last trimester of pregnancy [1,3,22–25]. A combination of pregnancy-induced changes (described in more detail below, and including engorgement, hypersecretion, hypermucosal edema, weight gain, and a reduction in functional residual capacity [FRC]) may predispose to snoring and UA obstructive events, due to UA narrowing during pregnancy [1–3,24–28].

The investigators of a recent study comprising two cross-sectional questionnaire surveys of 16 396 and 19 386 participants in Japan reported that pregnant women exposed to passive smoking are also prone to snore loudly and have breathing problems [29]. Another study of 469 pregnant women in the third trimester noted that smoking during pregnancy, together with pre-pregnancy weight, and age, was an independent risk factor for habitual snoring [11]. In total, 11.9% of these relatively young women (mean age 25.5±4.8 years) reported that they snored in the third trimester, compared with 2.5% of the same women prior to pregnancy, and 1.9% of non-pregnant women [11].

In a study recently reported by the present author [1], the women were slightly older (mean age 30±6 years in both healthy pregnant and preeclamptic women, and 31±7 years in non-pregnant women) than those mentioned above. Habitual snoring was noted in 35% of 167 healthy pregnant women, 59% of 82 preeclamptic pregnant women, and 17% of 160 non-pregnant women ($p<0.001$), as reported by both women and their bed-partners in the third trimester. Only 10% of both healthy pregnant and preeclamptic pregnant women snored habitually before pregnancy. Breathing pauses occurred at least occasionally in 18% of pregnant women, 35% of pregnant preeclamptic women, and only 6% of those who were not pregnant ($p<0.001$) [1].

In a cross-sectional study performed by Loube et al., 14% of 350 pregnant women attending "non-risk" antenatal clinics reported frequent snoring during the second or third trimesters, compared with 4% of 110 age-matched, non-pregnant women ($p<0.05$) [22]. Furthermore, Franklin et al. reported that 23% of 502 women who had just given birth snored often or always in the period leading up to the date of delivery [3]. Just 4% reported being habitual snorers before pregnancy. Another questionnaire study showed that the prevalence of recurrent and loud snoring in the mother increased non-significantly during pregnancy, from 5% before pregnancy to 10.4% in the third trimester, but decreased significantly after the delivery, affecting 4.4% of women [6]. Finally, in a prospective questionnaire study of 247 Chinese women performed by Leung et al., snoring was reported at frequencies of 29.7%, 40.5%, and 46.2% during the first, second, and third pregnancy trimesters, respectively [25]. The studies discussed above were limited by their cross-sectional design and reliance on the self-reporting of sleep complaints and smoking.

In a prospective study by Guilleminault et al., which aimed to evaluate the severity of snoring as scored by bed-partners during healthy pregnancy, snoring at least intermittently was reported for 18% of 267 women at the 6-week point, and 52% of 128 women 6 months into pregnancy [24]. The chronic loud snorers spent between 61% and 92% of TST with snoring.

Obstructive sleep apnea and oxygen desaturation during pregnancy and *post partum*

Using the Multivariable Apnea Prediction Index and the Epworth Sleepiness Scale, Pien et al. estimated that >10% of pregnant women may be at risk of developing obstructive sleep apnea (OSA) as pregnancy progresses [23]. However, the precise prevalence of OSA during pregnancy is unknown. Large, prospective studies using polysomnography (PSG) to investigate the relationship between pregnancy and OSA are needed. In lieu of these, the findings from a range of other studies on OSA and oxygen saturation in pregnancy are discussed below.

Many of the data on OSA during pregnancy come from a series of case reports, the findings of which are summarized in Table 1 [30–43]. Some of these reports suggest that pregnancy may precipitate or exacerbate OSA, especially in obese women. Complications such as pregnancy-induced hypertension (PIH) including pre-eclampsia, or low fetal birth weight developed in the majority of cases [30,32,34,35,37,40,43].

In a larger study, PSG was performed with an esophageal manometry test on a subgroup of 26 women after the 6th month of pregnancy; this selection comprised 13 loud snorers and 13 non-snorers [24]. None of these women had frank OSA, but airflow limitation and increased respiratory effort were common. In the same study, 13% of 267 pregnant women had arterial oxygen saturation (SaO_2) "drops" of ≥5% at least once during the night [24]. In a separate investigation, 12 pregnant women with pre-eclampsia risk factors (including obesity and chronic

Table 1. Summary of findings from case reports investigating OSA during pregnancy.

Study	Number of cases	Pregnancy complication	Method of diagnosis	AHI (events/h)	Treatment	Birth outcome
Brain et al. [30]	1	PIH	Clinical examination, PSG	30	CPAP	Growth restriction and fetal death
Charbonneau et al. [34]	1	Gestational diabetes	PSG	159	CPAP	Intrauterine growth restriction
Conti et al. [36]	1	Preeclampsia	Clinical examination	NA	None	Normal birth weight infant
Domingo et al. [42]	3	PIH (two women)	PSG	3, 16, 36	CPAP (one woman)	Cesarean sections (three women), healthy infants
Hastie et al. [35]	1	Gestational diabetes	PSG	42.5	Tracheostomy	Normal birth weight infant
Joel-Cohen and Schoenfeld [33]	3	None	Clinical examination	NA	None	One infant had intrauterine growth restriction, information on remaining births not available
Kowall et al. [37]	1	Preeclampsia	PSG	78.6	CPAP	NA
Langner et al. [43]	1	Preeclampsia	PSG	140	BPPV-ST, oxygen	Cesarean section at 31 weeks, two healthy premature infants (twins)
Lefcourt and Rodis [32]	1	Preeclampsia	Clinical examination	NA	None	Intrauterine growth restriction
Lewis et al. [40]	1	Pulmonary hypertension	Clinical examination	NA	Oxygen, CPAP	Normal birth weight infant
Pieters et al. [39]	1	None	PSG	0 (central alveolar hypoventilation)	NIPPV	Normal birth weight infant
Roush and Bell [31]	1	Preeclampsia	PSG	160	CPAP	Intrauterine growth restriction
Schoenfeld et al. [38]	8	None	Clinical examination	NA	None	All eight infants had intrauterine growth restriction
Taibah et al. [41]	1	Hypothyroidism	PSG	128	L-thyroxine	NA

AHI: apnea–hypopnea index; BPPV-ST: bi-level positive pressure ventilation in spontaneous/timed modus; CPAP: continuous positive airway pressure; NA: not applicable; NIPPV: nasal intermittent positive pressure ventilation; OSA: obstructive sleep apnea; PIH: pregnancy-induced hypertension; PSG: polysomnography.

hypertension) in the first trimester underwent PSG to identify sleep-related breathing abnormalities and had baseline blood pressure assessments [44]. None of the women had evidence of a clinically significant sleep apnea syndrome. The authors stated that all had significant SDB, as defined by a respiratory disturbance index (RDI) >3 events/h upon initial PSG. However, in pregnant women, inspiratory flow limitation index would be a better indicator of SDB than RDI, because in this population respiratory events may have different characteristics compared with those in patients with UA resistance syndrome (UARS) or OSA [16,45].

The relationship between obesity and gestational SDB was examined in a case–control study by Maasilta et al., who demonstrated that a normal pregnancy does not contribute to OSA in non-obese women [46]. However, in the same study the mean apnea–hypopnea index (AHI) of obese women increased significantly from 1.7 events/h in early pregnancy to 2.6 events/h in late pregnancy, although this increase was not clinically important. Preeclampsia and mild OSA occurred in only one obese mother [46].

In a case–control, longitudinal study performed by Edwards et al. [18], women with suspected OSA during late pregnancy were observed to have an AHI of 63±15 events/h and minimum overnight SaO_2 of 86%±2%. These measures improved markedly after delivery (AHI 18±4 events/h, SaO_2 91%±1%). Interestingly, all of the women in this study

were within 15 kg of the highest recommended weight for their height and stage of pregnancy [18].

Earlier data were contributed by Hertz et al., who reported that 12 healthy women had a small but significant reduction in nocturnal SaO_2 during the third trimester of pregnancy, compared with that during the *post partum* period [12]. In another study, arterial oxygen tension (PaO_2) measurements in the supine position during sleep were found to be significantly lower during pregnancy compared with during the *post partum* period [47].

Nikkola et al. assessed 10 women with multiple pregnancies and noted that there were no events of hypoxemia, nor was there significant OSA, in the third trimester of pregnancy [48]; in contrast, a report by Langner et al. outlined the case of a woman pregnant with twins who presented with severe OSA at 34 weeks' gestation (Table 1) [43].

Leung et al. performed PSG on eight of 247 pregnant women at 34 weeks' gestation [25]. None had evidence of significant OSA, and all had a minimum SaO_2 of ≥90% during the night. In their study, Brownell et al. also reported that there were no significant changes in oxygenation during sleep between 36 weeks' gestation and the *post partum* period, and that the prevalence of apnea and hypopnea was significantly lower during pregnancy compared with after delivery [49]. However, the subjects in these studies were healthy women with no evidence of SDB before the pregnancy. In each study, the investigators used a thermistor to measure respiratory airflow during PSG, which may have led to underestimation of the frequency of obstructive respiratory events [25]. Furthermore, selection bias may have occurred due to the small sample sizes.

Collectively, the findings from these studies suggest that women, especially those with predisposing factors such as obesity, may develop SDB during pregnancy, and that the severity of pre-existing OSA may be exacerbated as a result of pregnancy-related changes.

Pregnancy-related changes in breathing

Changes that increase the risk of SDB

Gestational weight and neck circumference

Gaining weight, with resultant obesity, is a main risk factor for SDB, and findings from a population-based, prospective cohort study strongly support this connection [50]. Pregnancy, weight gain, and physical inactivity, combined with other adaptations, may exacerbate pre-existing SDB or contribute to the development of SDB.

The results of previous studies highlighted that habitual snorers were significantly heavier than non-snorers, before and during pregnancy [2,3,11,23,25,26,46]. Leung et al. found that women with a baseline body mass index (BMI) of >25 kg/m^2 exhibited a significantly increased frequency of moderate-to-severe snoring intensity compared with those with a BMI of <25 kg/m^2 [25]. Pien et al. also reported that women with a higher baseline BMI and larger neck circumference during pregnancy reported more symptoms of OSA than others [23]. Additionally, case reports of OSA in pregnancy consistently involve obese women [30,31,38].

Weight gain is a risk factor for developing SDB [38,50–52], especially when associated with increased neck circumference in females [2,23,26,53]. Results from studies of non-pregnant women have also shown that the pharyngeal cross-sectional area and FRC increased with weight loss [50,51,54]. In a study involving the current author, snoring pregnant women had significantly higher pregnancy and pre-pregnancy weight and BMI compared with non-snoring women (by an average of +6 kg and +2 kg/m^2, respectively) [2]. Snoring pregnant women also had a tendency to have larger neck circumferences, being an average of 1 cm greater than in non-snorers [2]. Additionally, preeclamptic women, who had a high prevalence of SDB, had larger neck circumferences than healthy pregnant and non-pregnant women (by an average of +1 cm and +2 cm, respectively) [26]. In a recent cross-sectional study, neck circumference was also found to be an independent risk factor for PIH, including preeclampsia [11].

The fat deposition due to weight gain during or prior to pregnancy, especially fat within the soft tissue regions of the neck, could cause pharyngeal narrowing and contribute to SDB in pregnant women [2,38,50–52], or exacerbate existing SDB in pregnancy [55]. Imaging studies are still needed to clarify these issues.

Changes in the UA

In a study that utilized an imaging technique, women in the third trimester of pregnancy had a narrower UA than non-pregnant women [2]. Similarly, a semi-quantitative gross physical inspection has suggested that pharyngeal dimensions decrease during pregnancy, based on Mallampati scores in the first and third trimesters [27]. Engorgement, hypersecretion, and mucosal edema occur in the UA as a result of the progressive increases in estrogen and progesterone levels during pregnancy. These changes may lead to a reduction in pharyngeal and nasal dimensions [27,28,55] independent of any extrinsic compression of the airway.

Nasal obstruction is common during pregnancy. Increased blood and interstitial fluid volumes, and rhinitis of pregnancy (which occurs in 27–42% of women during pregnancy), are possible contributory factors [28]. Increased nasopharyngeal resistance may make airway pressure more negative during inspiration, and contribute to the collapse of the pharyngeal airway during sleep.

Elevated ventilatory drive as a result of increases in progesterone level may induce obstructive SDB by increasing diaphragmatic effort, leading to more-negative inspiratory pressures in the UA [56]. In turn, this may increase the tendency for the airway to collapse during sleep.

Sleep disturbance and fatigue are common complaints among pregnant women [4,8,12]. Both animal and human study results showed that sleep fragmentation and sleep deprivation decreased UA muscle activity and increased UA collapsibility [57,58]. The contribution of sleep disturbance and fatigue to the pathogenesis of SDB in pregnancy requires further study.

Changes in lung mechanics and blood gas tensions

A number of the physiological changes that occur during pregnancy affect lung mechanics, which, in turn, may alter blood gas tensions. Lung vital capacity and closing capacity have been shown not to change significantly during pregnancy [59–61]. As pregnancy progresses, the subcostal angle widens from 68° to 103°, leading to a compensatory increase in the anterior–posterior diameter of the chest [62]. These changes in chest configuration lead to tracheal shortening, and reductions in [51,59–62]:

- FRC (by 15–25%).
- Expiratory reserve volume (by 33–40%).
- Residual volume (by 22%).

Decreased FRC and tracheal shortening may cause small airway closures that contribute to SDB, especially in the supine position, due to gravity, tissue pressure, and loss of muscle tone during sleep [47,51,53,61,62]. The airway closure during normal tidal breathing results in ventilation–perfusion mismatch and reduced gas exchange in late pregnancy. Reduced FRC may also cause changes in arterial oxygen level, decreasing oxygen stores [60,63]. These changes increase the risk of hypoxemia and compromised oxygen delivery to the fetus [47,60,61,64].

Hyperventilation occurs due to increased progesterone levels. Minute ventilation is elevated by about 50% during pregnancy, accompanied by a 70% increase in alveolar ventilation [62,65]. Minute ventilation increases can overcompensate for the increased metabolic requirements of pregnancy, thus leading to respiratory alkalosis with a lower partial pressure of carbon dioxide (PCO_2) and a higher partial pressure of oxygen than normal [62,64]. Decreased arterial carbon dioxide tension ($PaCO_2$) during pregnancy could potentially induce periodic breathing at sleep onset, which has been shown to contribute to SDB [63,66]. These changes may result in respiratory instability and episodes of central sleep apnea during non-REM sleep [63,66].

Changes that reduce the risk of SDB

There are some factors that potentially might decrease the likelihood of oxygen desaturation and SDB during pregnancy. For example, high levels of progesterone will tend to cause hyperventilation, thus reducing PCO_2 at the central chemoreceptors [67,68] and tending to protect UA patency by increasing UA dilator muscle activity [69]. However, this might also cause airway narrowing, as mentioned above.

As normal pregnancy progresses from the 6- to 8-week stage to the 32- to 34-week period blood volume increases by 40–50%, with little change thereafter [65]. Increases in plasma and red cell volumes lead to this rise in intravascular volume. Cardiac output in the first trimester is 12–20% higher than in the non-pregnant state, and rises to an average of 50% above pre-pregnancy levels in the third trimester, while heart rate increases by approximately 29%, and stroke volume by around 18% [70]. Although an increase in circulating blood volume may cause nasal congestion, these changes in the cardiovascular system and a right-shifted oxyhemoglobin dissociation curve improve the delivery of oxygen to the placenta and maternal tissue [71].

In late pregnancy, women spend less time in the supine position, and more time in the lateral pose during sleep, which improves maternal cardiac output, stroke volume, and maternal and placental oxygenation [12,32,46,47,62]. Decreased REM sleep and recurrent awakenings during sleep in gestation [4,6,9,12] may also protect pregnant women from SDB events.

Pregnancy complications associated with SDB

Both case reports of OSA and epidemiological studies of SDB with pregnancy outcomes have reported that SDB during pregnancy is frequently associated with maternal and fetal complications such as PIH, pulmonary hypertension, preeclampsia, diabetes, and intrauterine growth restriction (Table 1) [30–32,35–37,40,72]. Some of these are discussed below.

Maternal complications

PIH is a generic term defined as repeated blood pressure recordings of >140/90 mmHg, first diagnosed after 20 weeks' gestation in previously normotensive women. If it is not accompanied by proteinuria, this condition is called gestational hypertension, but if it is, it is called preeclampsia [16,26,44,63,73]. A characteristic of hypertension normally associated with preeclampsia is the absence of the usual nocturnal dip in blood pressure, or a decrease in the day–night blood pressure difference, which is similar to the "non-dipper" pattern in OSA [16].

Franklin et al. showed that 14% and 10% of the women who snored habitually had PIH and preeclampsia, respectively, compared with 6% and 4% of non-frequent snorers [3]. Ursavas et al. also reported that 20% and 10.9% of pregnant women with habitual snoring developed PIH and preeclampsia, respectively, compared with 11% and 5.8% of non-snoring pregnant women [11]. However, it is not possible to draw any conclusions regarding cause and effect due to the cross-sectional designs of these questionnaire studies [3].

The current author found, in a study using objective methods, that women with preeclampsia had significantly narrower pharynxes, and larger neck circumferences during wakefulness, probably due to pharyngeal edema, than healthy pregnant and non-pregnant women [26]. Edwards et al. employed PSG with beat-to-beat blood pressure monitoring in preeclamptic women, none of whom had apnea or hypopnea [16]. They showed that UA flow limitations increased with characteristic low-frequency flow oscillations, affecting an average of 72% of breaths [16]. This is similar to the pattern of respiratory events found in UARS. However, it has been shown that in preeclamptic women, these episodes continue for several minutes rather than terminating by arousal, and are associated with blood pressure surges [5,16,74,75].

The abnormal respiratory events that occur during sleep in pregnancy may cause further increments in peripheral vascular resistance and systemic arterial blood pressure, as well as reductions in maternal cardiac output, in pre-eclamptic women [34,75].

Furthermore, there is growing evidence that the intermittent episodes of hypoxia and re-oxygenation associated with SDB can be a strong stimulus for oxidative stress [76], although this has been disputed by others [77]. These repeated changes in oxygen saturation could be considered analogous to recurrent episodes of placental hypoxia and reperfusion in preeclampsia, which causes endothelial dysfunction as a result of elevated production of oxygen free radicals [63,76,78,79]. Endothelial dysfunction may underlie intrauterine growth retardation and many of the manifestations of preeclampsia, such as peripheral vasoconstriction and abnormal regulation of blood vessel tone, in addition to high blood pressure [74,76,79].

Therefore, one could speculate that maternal hypoxia–reperfusion, caused by SDB, may exacerbate preeclampsia as a result of increasing the level of reactive oxygen species and the severity of endothelial dysfunction. In fact, a recent study by Yinon et al. reported that both SDB and endothelial dysfunction occur more often in women with preeclampsia than in women with uncomplicated pregnancies [80].

Youssef et al. analyzed all pregnancies found to be associated with OSA, gestational diabetes, or PIH (including those women with eclampsia and preeclampsia) in the 2003 Healthcare Cost and Utilization Project Nationwide Inpatient Sample data in the US [72]. They discovered that pregnant women with OSA were two times more likely to develop gestational diabetes than women with uncomplicated pregnancies after controlling for age, race, and obesity. Similarly, PIH was four times more likely in those with OSA [72].

Fetal complications

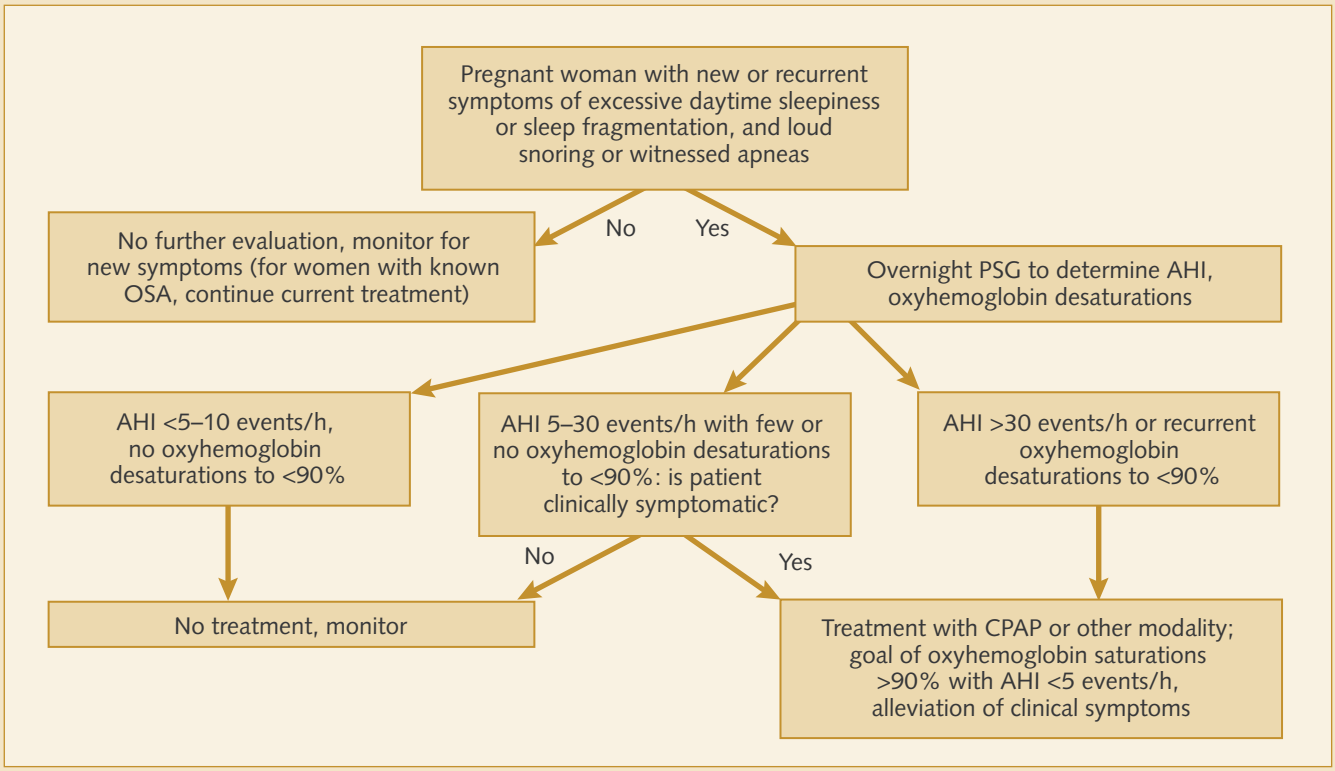
The effects of prolonged snoring on alveolar ventilation suggest that intermittent maternal hypoxia throughout many weeks of pregnancy can cause adverse outcomes in the developing fetus, including fetal growth restriction [31,33,34,38].

The secretion of many neurohormones, including the growth hormone produced during sleep, may be affected by sleep fragmentation due to obstructive events. In animal models, for example, it has been shown that gestational intermittent hypoxia leads to significant reductions in fetal growth [81]. Some case reports of pregnancy complicated by OSA and preeclampsia also indicate a possible connection of these with intrauterine growth retardation, fetal death, and fetal compromise [30–33,40].

In preeclamptic women, reduced placental perfusion combined with the impact of endothelial activation (both of which could be potentially exacerbated by SDB) may have an adverse effect on fetal development. Roush et al. reported that a witnessed apneic episode with maternal oxygen desaturation occurred in a preeclamptic patient concurrently with fetal heart-rate deceleration [31]. Joel-Cohen and Schoenfeld also reported fetal heart-rate abnormalities associated with maternal obstructive respiratory events during sleep [33]. In addition, Blyton et al. showed that there was a significant correlation between the cardiac output of preeclamptic women and fetal birth weight [75]. These authors proposed that a reduction in placental blood flow during maternal sleep may be specifically limiting to fetal growth and harmful to the well-being of the fetus [75].

In their study, Franklin et al. reported that habitual snorers were more than twice as likely as non-snorers to give birth to an infant with intrauterine growth retardation or with an Apgar score of <7 at both 1 min and 5 min [3]. After adjustment for maternal age, weight, and smoking habits, differences remained significant and the odds ratio for association with frequent snoring was 3.5 (95% confidence interval 1.3–9.4) for intrauterine growth retardation [3]. However, these findings were obtained from retrospective data, and recollection of symptoms may have biased the results.

Figure 1. Recommendations for pregnant women suspected of having OSA.



AHI: apnea–hypopnea index; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; PSG: polysomnography.
Adapted with permission from [63].

Conversely, Loube et al. reported that birth weight, Apgar score, and incidence of perinatal complications were not significantly different between the infants of women with and without regular snoring in the second or third trimester of pregnancy [22]. Likewise, Hedman et al. reported that there was not a significant relationship between snoring and infant birth weight in a prospective survey of sleep symptoms [6]; however, 52% of the subjects could not be followed up in this study.

Practical aspects of SDB in pregnancy

Assessment of symptoms

There is currently no consensus on the evaluation and treatment of SDB in pregnancy in patients with or without complications such as preeclampsia. However, Pien and Schwab made a series of recommendations for pregnant women suspected of having OSA, which are presented in Fig. 1 [63].

The cornerstones of the assessment process include careful history-taking and patient examination. Symptoms of SDB include snoring, witnessed apnea, and excessive sleepiness, and these can be monitored during pregnancy. Furthermore, factors predisposing to SDB can be examined in pregnant women, for example UA abnormalities, large neck circumference, and obesity [18,55]. Guilleminault et al. reported that physical examination of 12 pregnant women with OSA (diagnosed prior to pregnancy [n=7] or early in their first trimester [n=5]) revealed abnormal oropharyngeal anatomy, with a small oropharynx noted in all cases [55]. Women who do not have SDB before pregnancy but who have risk factors for SDB may require careful surveillance during gestation in order to detect the onset of the disorder, as it may develop as the pregnancy progresses [55].

Pien and Schwab suggest that pregnant woman with new or recurrent symptoms of excessive daytime sleepiness or sleep fragmentation, and loud snoring or witnessed apneas, should undergo an overnight PSG test to determine the AHI and characterize oxyhemoglobin desaturations (Fig. 1) [63]. Excessive daytime sleepiness is common in pregnancy and becomes increasingly common as pregnancy progresses [1,3,11,23]. However, sleepiness in pregnant women is not specific to SDB [1]. Many other factors, as described above, can cause it.

As mentioned, women with preeclampsia, even in the absence of OSA, have narrower UAs and higher incidence of inspiratory flow limitation than women with healthy pregnancies [16,26,45]. These women, and those with diabetes or a history of active or passive smoking may be

closely evaluated for the presence of SDB [72]. Women with preeclampsia do not necessarily demonstrate more sleepiness than healthy pregnant women [1]. Thus, in the clinical setting, questions should extend beyond simply asking about a patient's sleepiness, and should instead focus on other symptoms of SDB. If SDB is present, blood pressure and blood glucose levels should be closely monitored.

Currently, PSG is not recommended for cases of simple snoring, preeclampsia, or intrauterine growth retardation [63]. Therefore, with the exception of patients with obvious signs and symptoms of OSA, patients with mild-to-moderate SDB may be underdiagnosed in the pregnant population.

Prevention of SDB during pregnancy

In all pregnant women, the lifestyle modifications that are suggested to patients with OSA, such as avoidance of excessive weight gain and of sleeping in a supine position, can prevent SDB [47]. Overweight women considering pregnancy should be informed about the risks of obesity in gestation and advised to lose weight before pregnancy in order to improve their health and to decrease the risk of SDB during gestation. The findings from a population-based study indicated that public health programs resulting in even modest weight control reduce the prevalence of SDB [50]. Thus, a regular, antenatal exercise program can be beneficial in both overweight and normal women to prevent them gaining excessive weight and developing SDB. In addition to these suggestions, exercise may improve sleep quality and guard against sleep deprivation, which causes a reduction in UA muscle activity [57].

Non-invasive treatments that focus on relieving nasal congestion, such as nasal saline washes or nasal dilators, may prevent the collapse of the pharyngeal airway during sleep. Educational programs emphasizing the adverse effects of active and passive smoking and alcohol consumption during pregnancy could improve sleep hygiene and prevent SDB [29,64].

Treatment of SDB

Pregnant women with known SDB prior to pregnancy can continue their current treatment [63]. However, the condition may need to be reassessed, particularly in the third trimester of their pregnancy, because the severity of the condition can be exacerbated with weight gain [18]. Those women with position-dependent apnea–hypopnea, without significant oxyhemoglobin desaturations or hypertensive complications, may possibly benefit from sleeping in the lateral *decubitus* position [47,63].

Continuous positive airway pressure (CPAP) therapy has been successfully used for pregnant women with OSA, severe dyspneic attacks, and preeclampsia [16,34,36,37,55]. Pien and Schwab recommend treatment with CPAP or other therapies if a pregnant woman meets one of the following conditions:

- An AHI of 5–30 events/h with few oxyhemoglobin desaturations of <90%, and clinical symptoms.
- An AHI of >30 events/h.
- Recurrent oxyhemoglobin desaturations of <90% (Fig. 1) [63].

The main aim of these treatments is to obtain oxyhemoglobin saturations of >90%, an AHI of <5 events/h, and alleviation of clinical symptoms. However, this treatment plan is not evidence-based.

CPAP pressure may require readjustment due to moderate worsening of SDB as a result of uterine enlargement and fetal growth during pregnancy. For example, in a study of 12 pregnant women diagnosed with SDB in early pregnancy, six needed an increase in CPAP pressure after 6 months' gestation [55]. Adherence to CPAP treatment was very good, at >80%. Home monitoring during the 8th month of gestation demonstrated normal SaO_2 during sleep and the absence of apnea, hypopnea, and tachypnea [55].

CPAP has been used in several studies of women with preeclampsia. In one of these, which assessed 11 women, CPAP abolished inspiratory airflow limitation, significantly reduced nocturnal blood pressure, and improved nocturnal oxygenation [16]. It should be noted, however, that this study had no control group. Treatment and non-treatment nights were not randomized, and daytime blood pressure was not measured to determine whether the effect of CPAP was continued [16].

In a second study, which was a randomized controlled trial of nasal CPAP in 24 women with severe preeclampsia, the data indicated that sleep is associated with adverse hemodynamic changes in preeclampsia [75]. CPAP treatment decreased mean arterial pressure (MAP) between wakefulness and sleep by 3 mmHg, and reversed the decrease in cardiac output during sleep witnessed without CPAP. Thus, improving cardiac output and MAP during sleep may reduce the risk of intrauterine growth retardation associated with preeclampsia [75]. It should be noted that, in this study, true randomization was not performed; instead, every second subject was allocated to receive the treatment.

Two recent studies by Guilleminault et al. and Poyares et al. evaluated the potential benefit of nasal CPAP usage in pregnant women with preeclampsia risk factors early in pregnancy [44,82]. In a prospective, longitudinal study, 12 women with either chronic hypertension or obesity were recruited in their first trimester and used CPAP throughout pregnancy [44]. Women with chronic hypertension did not develop preeclampsia and did not need to increase their

Table 2. *Post partum* recommendations for women with pregnancy-associated OSA.

	Initial *post partum* management	If symptoms recur with withdrawal of therapy, or weight gain persists
Mild-to-moderate pregnancy-associated OSA	*Post partum* withdrawal of therapy with close follow-up for symptom recurrence; if asymptomatic, monitor for recurrence in future pregnancies	Obtain overnight PSG results to determine baseline AHI; assess need for treatment and therapeutic options based on findings
Severe pregnancy-associated OSA	Continue therapy and obtain overnight PSG results when weight within 10–15% of baseline to rule out persistent OSA	Obtain repeat overnight PSG results to establish baseline AHI (consider split-night study with CPAP titration) and need for continued therapy
Pre-existing OSA	Consider return to pre-pregnancy therapy when weight within 10–15% of baseline, with close follow-up for symptom recurrence	Repeat overnight PSG (with split-night study if using CPAP at baseline) to determine new baseline AHI; modify pre-pregnancy therapy based on findings

AHI: apnea–hypopnea index; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; PSG: polysomnography.
Adapted with permission from [63].

dosage of antihypertensive medication, but one of the obese women had preeclampsia. Nasal CPAP was well-tolerated in all hypertensive women, and nightly compliance with CPAP usage was good. CPAP re-titration was required in all subjects [44]. In a randomized, controlled trial of women with chronic hypertension and snoring, nasal CPAP usage combined with standard prenatal care during the first 8 weeks of pregnancy provided better blood pressure control and improved pregnancy outcomes, compared with standard prenatal care alone [82]. None of the women in the CPAP group (n=7) developed preeclampsia, but one of the control subjects (n=9) did [82]. Even though these two studies had certain limitations, such as small sample sizes, the results are promising.

Collectively, this evidence suggests that CPAP cannot treat the underlying cause of preeclampsia, but decreases blood pressure and thus potentially allows the pregnancy to proceed for longer, ensuring greater fetal maturity at delivery. However, the results of these studies should be interpreted carefully due to their limitations, and thus there is a need for larger, randomized controlled trials investigating the effect of CPAP on SDB and blood pressure in preeclampsia. In the present author's view, CPAP use in the treatment of preeclampsia should not be recommended at present.

Treatment with supplemental oxygen may be considered for pregnant women with SDB who are unable to use therapies such as CPAP. In severe cases associated with obesity, twin pregnancy, and other conditions, bi-level positive pressure ventilation therapy may be more successful than CPAP [43]. Additionally, combination therapy with CPAP or bi-level positive pressure ventilation plus oxygen supplementation would seem to be a more satisfactory treatment option than using one of them alone [37,40,43].

Tracheostomy has been performed in a pregnant woman with OSA, but the case described by Hastie et al. is an unusual example [35]. The technique is generally used for severely compromised cases.

Management of pregnancy-associated SDB after delivery

It has been reported that the severity of SDB subsides after delivery [2,12,18,24,37,47]. Thus, a *post partum* PSG is necessary after weight stabilization (e.g., ≥3 months after delivery) to detect whether SDB persists in these women. Pien and Schwab have provided some *post partum* recommendations for women with pregnancy-associated OSA (Table 2) [63].

Conclusions and future directions

Symptoms of SDB are common among pregnant women, due to a range of pregnancy-related changes in the respiratory system. SDB in pregnancy is associated with maternal–fetal complications, including preeclampsia and intrauterine growth retardation. Clinical predictors of SDB need to be established in pregnant women. Screening by sleep questionnaire during the patients' routine antenatal visits may help to detect possible sleep disorders in these women. A pregnant woman with loud snoring or witnessed apneas, excessive daytime sleepiness, or sleep fragmentation might be offered an overnight PSG test. Guidelines for the treatment of pregnancy-associated SDB need to be developed, and the use of CPAP as a therapy in pregnancy requires further study.

Disclosures

The author has no relevant financial relationships to disclose.

Acknowledgment

The author would like to thank to Professor Neil Douglas for his valuable advice, support, and encouragement.

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IN FOCUS

Conceptualizations of Sleepiness and the Measurement of Hypersomnia

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Excessive daytime sleepiness is a burgeoning health concern that is linked with a series of negative consequences, including impaired cognitive function and an increased likelihood of automobile accidents. Sleepiness itself can be conceptualized as "introspective," "manifest," or "physiological." These distinct forms of sleepiness are quantified using different assessments. For example, introspective sleepiness is a subjective, self-reported measure, recorded using instruments such as the Epworth Sleepiness Scale, while physiological sleepiness is an objective measure of underlying sleep drive, obtained using methods such as the Multiple Sleep Latency Test. This article aims to assist the practitioner in distinguishing the different concepts of sleepiness and the methods used to quantify them. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(3):106–11.

Consequences and prevalence of excessive sleepiness

Sleepiness is a state of basic physiological need [1], and hypersomnia or excessive sleepiness can be defined as the presence of sleepiness in situations that a person should normally be alert in. Excessive daytime sleepiness is a growing health concern, and the dangers it poses are becoming increasingly apparent.

Firstly, excessive sleepiness has a negative impact on family life [2]. Furthermore, the automobile accident rate is increased almost seven-fold among patients with excessive sleepiness [3]. Interestingly, most automobile accidents occur in the early morning hours, a time when the fewest vehicles are on the road. This high accident rate makes sense when the fact that sleepiness is greatest at this time is considered [4]. As a result of chronic sleep deprivation, medical residents comprise a particularly sleepy subpopulation. Survey data show that this population has a much higher incidence of medical errors and sleepy driving when compared with medical faculty members who get more sleep [5,6]. Finally, cognitive functioning is impaired as a result of sleepiness [7].

The prevalence estimates of sleepiness vary widely depending on the definition of excessive sleepiness used and the population studied. However, with the standardization of sleepiness scales and the development of physiological tests of sleepiness, such prevalence statistics are becoming easier to calculate [8,9].

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In a recent study involving a large, random sample from southeastern Michigan, USA (n=1648), the prevalence of excessive sleepiness estimated by physiological testing was 13% [10]. In contrast, the prevalence of sleepiness in the same sample estimated using a self-assessment scale was 20%.

Factors affecting daytime sleepiness

The function of sleep is presently unknown and how much sleep individuals "need" is difficult to pinpoint. Human sleep need has, however, been investigated in a number of studies. In an analysis by Wehr et al., healthy young adults were allowed to remain in bed for 14 h each night, over a period of 4 weeks [11]. Towards the 4th week, their average time asleep became "asymptotic" at 8.2 h, with little variability between individuals; thus, the average sleep requirement for young adults in a 24-h period is thought to reflect this value.

Various factors have been shown to be associated with the risk of developing excessive sleepiness, including the number of hours of sleep obtained per night, employment and marital statuses, snoring, and depression [12]. In a study by Breslau et al., young adults were found to be generally sleep-deprived, with the average young adult getting 6.7 h of sleep during weeknights and 7.4 h per night at the weekend [12]. Employment and marital statuses were related to the number of hours of sleep and thus also to the risk of sleepiness (single status and no employment being associated with more sleepiness than married status and full- or part-time employment, respectively). Additionally, both depression and self-reported snoring were linked with excessive sleepiness [12].

Self-reported versus physiological sleepiness

The presence or absence of excessive sleepiness, as well as its intensity, can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and sleep duration. However, the self-reported, subjective experience of sleepiness can be reduced under conditions of high motivation, excitement, and exercise; that is, physiological, or objective, sleepiness may not necessarily be manifest. This phenomenon is called "masking," and is typified by the results of Bonnet et al., who demonstrated that average sleep latencies recorded using the Multiple Sleep Latency Test (MSLT; a measure of physiological sleepiness) were increased by 6 min when sitting on, as opposed to lying in, a bed [13]. However, as physiological sleepiness increases in monotonous, sedentary situations, the likelihood of sleep onset, and thus also of micro-sleeps, is heightened [14,15].

In contrast, a physiologically alert person does not experience sleepiness or appear sleepy even in the most soporific situations [1]. Thus, despite popular notions, heavy meals, warm rooms, boring lectures, and the monotony of long-distance automobile-driving only "unmask" underlying physiological sleepiness when it is present, rather than causing it.

Another notable quality of excessive sleepiness is the disconnect that exists between self-reported sleepiness and physiological sleepiness. Simply put, many individuals are not aware of how physiologically sleepy they are. In fact, this disparity increases as sleepiness increases in severity [16,17]. This phenomenon has been ascribed to a chronic, adaptive process.

Quantifying sleepiness

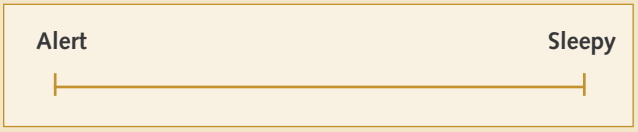
Traditionally, when healthcare professionals discuss "measuring sleepiness," they do so under three headings [1]:

- Introspective sleepiness.
- Manifest sleepiness.
- Physiological sleepiness.

"Introspective sleepiness" refers to self-reported, subjective sleepiness, and is a patient's assessment of his or her internal state. In contrast, "manifest sleepiness" refers to the deficits in performance, behavior, or both that result from sleepiness. Finally, "physiological sleepiness" reflects a person's underlying sleep "drive," and is an objective measure of sleep propensity. This article explores this conceptual model of sleepiness, and examines how each of these phenomena is measured.

As manifest and self-reported sleepiness can be masked, it is valuable for the clinician to remember that these indicators often underestimate physiological sleepiness. However, as with the results of any other medical test, assessments of sleepiness must always be viewed within the broader context of an individual's clinical history and the findings of other examinations. Furthermore, while not within the scope of this article, it is important for clinicians to remember that, depending on its cause, there are numerous methods for addressing excessive sleepiness, including non-pharmacological approaches, such as napping and caffeine consumption, and pharmaceutical treatments, such as stimulants (e.g. methylphenidate) and wakefulness-promoting agents (e.g. modafinil).

Figure 1. A Visual Analogue Scale with "sleepy" and "alert" endpoints. The participant is asked to mark the point along the line that best describes his or her current internal state of sleepiness.



Introspective sleepiness

Various instruments have been used to measure self-reported sleepiness. Most of these are self-rating scales that do not require a sleep laboratory visit, and can be easily administered in a doctor's office. The most commonly used scale is the Epworth Sleepiness Sclae (ESS), which will be described in the greatest detail; other instruments utilized include Visual Analogue Scales (VASs), the Stanford Sleepiness Scale (SSS), and the Profile of Mood States (POMS).

Before considering these scales in detail, it is important to differentiate self-reported sleepiness from fatigue. Sleepiness and fatigue are conceptually distinct, but are pervasively confounded in clinical and research settings, as well as in everyday spoken language. Fatigue can be mental in nature when associated with depression, or physical in nature when associated with body weakness. It is a common symptom associated with many physical ailments, and may be a side effect of medications. Furthermore, it may respond to lying down or resting. In contrast, "true" sleepiness will be ameliorated only by sleep [1].

The POMS, VASs, and SSS

The POMS was originally designed to measure mood, but in the research setting it is often used to record characteristics of sleep [18]. Sleepiness impacts upon on several POMS subscales, including Vigor, Confusion, and Fatigue [19].

A commonly used VAS comprises a 100-mm line anchored by two endpoints, which denote "sleepy" and "alert" (Fig. 1). The patient is asked to mark a point along the line that best describes his or her current internal state of

sleepiness. The use of VASs in sleep research has been discussed by Herbert et al. [20].

For many years, the SSS was the standard measure of introspective sleepiness [21]. Individuals choose one of seven presented statements in the scale to describe their current state of sleepiness, with statements ranging from "Feeling active and vital, alert, wide awake" to "Almost in a reverie, sleep onset soon, lost struggle to remain awake."

From the brief descriptions provided above, it is important to understand that both VASs and the SSS record sleepiness at the present moment. These scales can therefore be used to detect sleepiness as it waxes and wanes throughout the course of a day. In research settings, one of these tests can be used prior to each nap in the MSLT.

Both the SSS and VASs are easy to administer in practice. The results obtained on both scales are affected by sleep deprivation [21], but normative data are not available for them.

The ESS

The ESS was developed at the Sleep Disorders Unit of Epworth Hospital (Melbourne, VIC, Australia) in 1991 [22]. In contrast to VASs and the SSS, it measures sleep propensity rather than sleepiness at the present moment. The ESS is a validated sleep questionnaire that presents the patient with eight different situations, which are listed in Table 1. Participants are asked to rate, on a scale of 0 to 3 (where 0 = "none," 1 = "slight," 2 = "moderate," and 3 = "high"), their chance of "dozing off" in each circumstance based on the 2 weeks prior to the assessment. Total ESS scores can therefore range from 0–24, with scores between 0 and 10 representing normal values.

The situations described in the ESS are monotonous and sedentary. As such, they are intended to unmask latent sleepiness. Furthermore, as the individuals completing the ESS are rating their drive to sleep, or sleep propensity, they make judgments about their probability of falling asleep, rather than describing their current internal state.

Johns conducted validity and reliability studies on the use of the ESS, for example measuring sleepiness in patients with sleep-disordered breathing before and after treatment with continuous positive airway pressure (CPAP) [22,23]. The elevated mean ESS score recorded prior to treatment (14.3) was reduced following CPAP (7.4), falling within the normal range. While ESS scores have been found by some investigators to correlate with the severity of obstructive sleep apnea (OSA) [24], in the author's clinical experience, some subjects with severe OSA do not complain of excessive daytime sleepiness, whereas some with moderate OSA do. This may be a result of the aforementioned adaptive process.

In a recent study of 470 healthy adults, mean and median ESS scores were 6.9 and 6.0, respectively [25]. ESS scores were not significantly associated with age, gender, or body mass index. Approximately one-quarter of the sample reported sleepiness (i.e. an ESS score of ≥10).

Table 1. The Epworth Sleepiness Scale.

Use the following scale to choose the most appropriate number for each situation: **0 = Would never doze** **1 = Slight chance of dozing** **2 = Moderate chance of dozing** **3 = High chance of dozing**	
Situation	**Chance of dozing**
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____
Total	_____
Scores: **0–10 = Normal range** **10–12 = Borderline abnormal sleepiness** **12–24 = Abnormally sleepy**	

Adapted with permission from [22].

In summary, the ESS is the most commonly used scale for the measurement of self-reported sleepiness, and normative data are available for it. Furthermore, there is slight but statistically significant correlation between the results of the ESS and those of the MSLT, the objective test for sleep drive [26]. However, further research is needed to define the effects of age, sleep deprivation, medications, and circadian rhythms on ESS scores.

Manifest sleepiness

Another method for assessing sleepiness is to measure its effect on an individual's performance in various tasks. Such tests are usually carried out in the laboratory setting for research purposes, and most are based on the principle that long, externally paced, and monotonous tasks that unmask sleepiness are sensitive to sleep loss. Thus, they attempt to measure the cognitive slowing, inattention, or impaired reaction times that may occur as a result of hypersomnia.

There are several such tests available. The Psychomotor Vigilance Test (PVT) was developed by Dinges et al. at the University of Pennsylvania (Philadelphia, PA, USA) [27,28]. It consists of giving 10-min, sustained-attention tasks to the participant, during which a hand-held, computerized display-and-response unit quantifies the response latency to multiple light-emitting diode (LED) stimuli. Results obtained using the PVT correlate with those of the MSLT, and the results are sensitive to sleep deprivation [27].

Another widely used test is the Oxford Sleep Resistance Test (known as the OSLER) [29], which consists of four 40-min tasks during which LED stimuli are presented, and patient responses are measured. The results obtained are sensitive to hypersomnia.

From this brief overview, the key message is that using these predominantly research-based assessments, investigators can attempt to mimic monotonous situations that unmask latent sleepiness.

Physiological sleepiness

Objective tests are used to assess physiological sleepiness; the relevant instruments provide a measure of the rapidity of sleep onset or sleep tendency, and therefore assess sleep drive. Into this category fall the MSLT, the Maintenance of Wakefulness Test (MWT), pupillometry, and electro-encephalography (EEG). Of these, the MSLT will be described in the greatest detail. Pupillometry and EEG are discussed for historical interest only, as they are not often used in current research or clinical settings.

Pupillometry and EEG

As pupil stability and size are affected by an individual's level of arousal, observation of the pupillary constriction that occurs at sleep onset can be used as a measure of sleep tendency [30]. In fact, it was used in the assessment of narcolepsy by a small number of laboratories prior to the development of the MSLT [31]. Although pupillometry can now be performed electronically, the technique is not popular as a clinical test as it is time-consuming, and it has been superseded by the MSLT. Additionally, there are no normative pupillometry data available.

Computerized, quantitative analysis of EEG waveforms, with the aim of identifying increased delta activity as a marker of sleepiness, has been attempted [32,33]. However, as with pupillometry, this technique is time-consuming and no normative data exist.

The MSLT

The MSLT, when applied following overnight polysomnography (PSG), is the "gold standard" method for measuring physiological sleepiness. Developed by Carskadon et al. in 1982, it consists of giving patients a series of five nap opportunities in a quiet, dark room at 2-h intervals, beginning 2 h after waking up from a nocturnal PSG test [1]. The average sleep latency from these five naps yields the "MSLT latency," which is a measure of physiological sleepiness. The nocturnal PSG test is performed to identify the presence of OSA or any other pathology that might contribute to sleepiness. In addition, the quality of overnight sleep (as described polysomnographically by sleep latency as well as sleep efficiency) can affect MSLT latency; the PSG recording is thus useful additional information for evaluating physiological sleepiness [34].

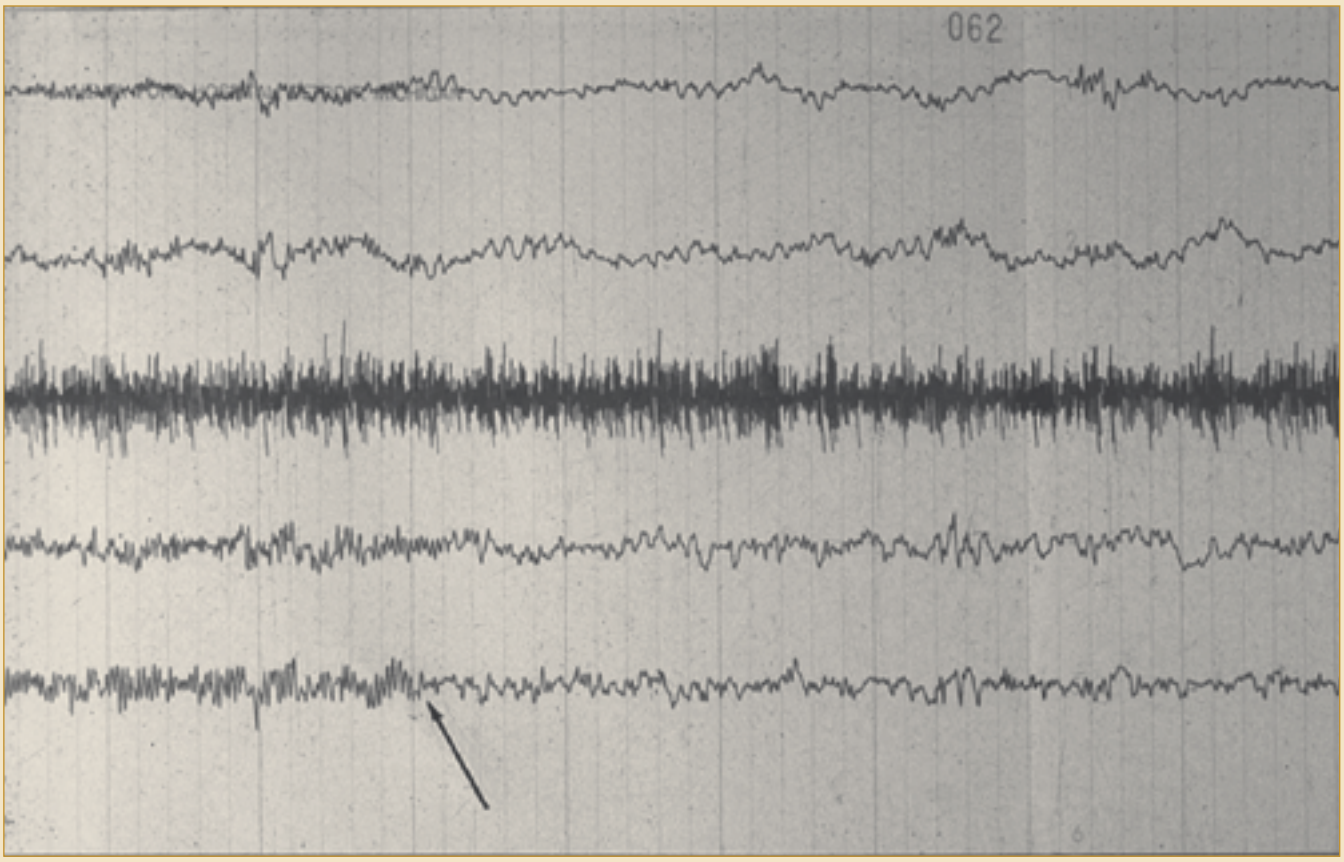
Patients are tested under standardized conditions, and in their "street" clothes. They are instructed to "try to fall asleep" [8]. The minimal electrophysiological parameters required for the test are right and left electro-oculograms, occipital and central EEG scans, and the chin electro-myogram. In some laboratories, additional measurements of snoring and respiratory flow are recorded. Sleep onset is defined as either "three epochs of stage one sleep" or "one epoch of stage two, three, four, or rapid eye movement [REM] sleep" (Fig. 2) [35,36].

Two protocols exist for conducting an MSLT, based on whether the test is being performed on a clinical or research basis. In the clinical setting, the test session is allowed to continue for ≥15 min after sleep onset to allow for the commencement of REM sleep. If no sleep occurs, the nap session is terminated after 20 min. In contrast, in the research setting, each nap session is terminated after sleep onset. Thus, no accumulation of sleep is allowed. However, if no sleep onset occurs then the nap session is terminated after 20 min as in the clinical protocol [35,36].

Normative data exist for the MSLT; among otherwise healthy adults, mean latencies of 10.4 min and 11.6 min were reported by Littner et al. for the four- and five-nap protocols, respectively [35]. Pathological sleepiness has been defined as a mean latency of ≤5 min [34]; however, the current International Classification of Sleep Disorders coding manual defines an abnormally short MSLT latency (such as that observed in narcolepsy or idiopathic hypersomnia) as <10 min [37]. Using the latter definition, one would expect the estimated prevalence of excessive sleepiness in population-based samples to be higher than when using the former. Additionally, the presence of ≥2 REM sleep episodes during the MSLT, together with excessive daytime sleepiness and cataplexy, is diagnostic for narcolepsy [38].

Mean latency as measured by the MSLT is a good reflection of sleep drive, and sleep deprivation causing sleepiness will result in a reduced latency [34]. Circadian influences can also be observed using the MSLT, with lower nap latencies observed during the afternoon nap sessions [39].

Figure 2. Polysomnography recording obtained during a Multiple Sleep Latency Test. This 30-s epoch exhibits sleep onset. (Arrow denotes the point where sleep onset occurs – alpha activity is replaced with stage-two sleep.)



Description of traces (top–bottom): right electro-oculogram (EOG); left EOG; chin electromyogram; central electroencephalogram (EEG); occipital EEG.

The MWT

The procedures used in the MWT are similar to those employed in the MSLT, with the major difference being in the instruction given to the test subject, who is told to "attempt to remain awake." Thus, the test is used to assess an individual's capability to not be overwhelmed by sleepiness – the functioning of the underlying wakefulness system is examined. As there is no direct way of measuring "wake drive," this is estimated by how long it takes the participant to fall asleep under these conditions, which mirror those in which sleep onset occurs inadvertently when a person is passive and sedentary in a non-stimulating environment. In fact, as a result of the differing instructions, in studies comparing the MWT with the MSLT, the sleep latencies recorded with the two tests differ [40,41].

During the MWT, the individual is monitored for EEG sleep onset during 4–6 sessions, scheduled at 2-h intervals beginning 2 h after awakening from the previous night's sleep. In the past, a major criticism of the MWT related to the wide variety of protocols that were employed. Initially, MWT session-length was not well standardized, and 20-, 30-, and 40-min tests were used, with the longer tests devised to avoid ceiling effects. However, the American Academy of Sleep Medicine's Standards of Practice Committee has now developed practice parameters for clinical use of the MWT that are based on a critical review of the literature as well as expert opinion [36].

Based on these recommendations, use of the MWT is indicated when assessing individuals whose inability to remain alert constitutes a safety hazard, and in patients with narcolepsy (or idiopathic hypersomnia) to determine their response to pharmacotherapy. For example, a four-session, 40-min version of the test is recommended when the issue is personal or public safety [36].

Based on statistical analysis of normative data performed by Doghramji et al., a mean sleep latency of <8 min on the 40-min MWT is abnormal [42]. Scores between 8 min and 40 min (the maximum value) are of uncertain significance. In that study, the mean sleep latency for presumed healthy volunteer subjects was 30.4 min. The strongest evidence for an individual's propensity to maintain wakefulness is provided by his or her ability to remain awake throughout all

sessions of the 40-min test; in the results of Doghramji et al., this corresponded with the upper limit of the 95% confidence interval. However, even in cases where 40-min MWT sleep latencies are collected for an individual, clinical judgment remains critical in assessing sleepiness, as normal values do not necessarily guarantee safety [43].

Practical considerations and conclusions

This article has reviewed a number of methods for measuring sleepiness. The decision as to which test is most appropriate in a given scenario is often based on multiple factors. For example, it should be considered whether the assessment is being conducted for clinical assessment, research, or legal purposes. In the clinical setting, sleepiness can be investigated with the ESS, which is an office-based, "paper-and-pencil" test. Excessive sleepiness can then be explored further in a sleep laboratory using the MSLT. Furthermore, the MWT is a good method for assessing patients in whom treatments for excessive sleepiness require evaluation.

In the research setting, the choice of test employed will depend on the research agenda. In this scenario, the PVT is a popular method for measuring the deficits resulting from sleepiness.

In the author's experience, sleep specialists are being asked to render opinions in legal cases concerning "fitness for duty" with increasing frequency. A patient may have an interest in appearing sleepy or alert in such cases, and the MSLT and the MWT are critical tools to assist the healthcare professional in forming an opinion.

The search for a blood test to measure accumulating sleepiness that is simple and non-expensive has yet to bear fruit. As such, measuring sleepiness in the clinical setting is a complex matter. In conclusion, in the doctor's office, subjective sleepiness can be detected using the ESS, whereas in the sleep laboratory, overnight PSG followed by the MSLT is the gold standard for measuring sleepiness objectively.

Disclosures

The author has no relevant financial relationships to disclose.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

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

INSOMNIA

Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations

Walsh JK, Krystal AD, Amato DA et al.
Sleep 2007;**30**:959–68.

The current article describes a double-blind, placebo-controlled study in which patients with primary insomnia were randomized to receive eszopiclone or placebo for 6 months. The eszopiclone group exhibited decreased self-reported insomnia severity, increased self-reported sleep, reduced self-reported work limitations, and enhanced self-reported quality of life compared with the placebo group.

The investigation described in the current article was the first placebo-controlled study of chronic primary insomnia to demonstrate long-term improvements in a variety of self-reported daytime *sequelae* associated with chronic insomnia.

Using advertisements and physician referrals, men and women with primary insomnia (defined according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*), prolonged latency to sleep onset (>30 min), or decreased hours of sleep (<6.5 h) were recruited to this 6-month randomized, double-blind study of nightly eszopiclone (3 mg/night). Patients received either eszopiclone or placebo every night for 6 months, followed by sudden substitution of placebo for eszopiclone for an additional 14 nights. Data were collected during patient visits at screening, baseline, 6 months, and at study end. Additionally, an Interactive Voice Response System was used to collect further information at several time points during the study.

Outcome measures included self-reported sleep latency, wake after sleep onset, total sleep time, number of awakenings, sleep quality, daytime alertness, ability to concentrate, ability to function, and physical wellbeing. Other outcome measures included the Insomnia Severity Index (ISI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Short Form-36 (SF-36) Health Survey, and the Work Limitations Questionnaire (WLQ). Adverse events were monitored throughout the study.

Of the 830 patients included in the study, 280 were randomized to placebo and 550 were randomized to eszopiclone. The placebo drop out rate was 52%, compared with 37% for eszopiclone. Two patients in the eszopiclone group did not receive the agent and were not included in the analysis.

Improvements in all measures of self-reported sleep and daytime function were demonstrated throughout the entire 6-month study period in patients on eszopiclone and the effect size was large. ISI scores were similar at baseline but were significantly lower after this point in the eszopiclone group. Comparable results were obtained using the FSS and ESS. WLQ scores were similar at baseline but showed consistent improvements across all domains for the eszopiclone group after baseline, compared with placebo. Improvement was also noted on the SF-36 with eszopiclone. The authors observed no apparent "rebound" insomnia after discontinuation of treatment. Adverse events were considered to be mild or moderate but were more prevalent in the eszopiclone group (75.7% vs. 58.9%; $p<0.05$).

The authors conclude that these findings support the efficacy of long-term treatment with eszopiclone in primary insomnia patients, with improvements in symptoms of insomnia and associated daytime dysfunction. However, they suggest that these results apply only to patients with primary insomnia, and propose that similar studies should be performed in patients with insomnia associated with other comorbid illnesses. Finally, they highlight important limitations to this study, namely the high drop-out rate and the fact that polysomnography was not performed.

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Long-term nightly treatment with indiplon in adults with primary insomnia: results of a double-blind, placebo-controlled, 3-month study

Scharf MB, Black J, Hull S et al.
Sleep 2007;**30**:743–52.

In this 3-month, industry supported, placebo-controlled trial, subjects with primary insomnia who took indiplon at a dose of 10 mg or 20 mg experienced improvements in sleep (shorter latency to sleep onset, and improved sleep maintenance and duration), daytime functioning, and quality of life, compared with those receiving placebo.

Primary insomnia is a common sleep disorder, and is associated with impaired quality of life in many domains. The numerous etiologies of insomnia can act singly or in combination, and include psychiatric, genetic, stress, environmental, and circadian factors, other intrinsic sleep illnesses (such as restless legs syndrome and obstructive sleep apnea), medical illnesses, and drug or medication use. Treatment of insomnia typically involves sleep hygiene education, cognitive–behavioral therapy, and the use of pharmacological agents, in particular benzodiazepine receptor agonists.

The study described in the current article was designed to test the effects of a new benzodiazepine receptor agonist, indiplon (a pyrazolopyrimidine), which has a high affinity and selectivity for the α1-subtype of the γ-aminobutyric acid A receptor complex in patients with primary insomnia.

The study was conducted at 64 sites in the US, Canada, and the UK. Eligible patients completed a 3-week, single-blind placebo lead-in after undergoing a drug-free screening period of 1–2 weeks. Sleep diaries were kept and at the third visit (baseline) participants were randomized in a 1:1:1 ratio to one of three double-blind treatment arms (indiplon 10 mg, indiplon 20 mg, placebo). At the end of the 3-month treatment period, indiplon was abruptly discontinued and a placebo substituted (single-blind) for 1 week. Outcomes were assessed using sleep diaries and additional patient-reported sleep parameters.

Additional data were collected at each patient assessment visit using the Medical Outcome Study sleep scale, the Insomnia Severity Index (ISI), the Investigator Global Rating of Severity scale, and the Investigator Global Rating of Change instrument. Discontinuation symptoms were assessed using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) at pretreatment baseline, at the end of double-blind treatment, on days 1 and 2 of the sudden discontinuation period, and at the final visit.

In all, 702 of 2029 screened participants were randomized: 236 to indiplon 10 mg, 233 to indiplon 20 mg, and 233 to placebo. The drop-out rate was high in all groups: 41.1% in the indiplon 10 mg group, 51.9% in the indiplon 20 mg group, and 50.6% in the placebo group. The reasons for dropping out were remarkably similar in all groups with the exception that 19.7% of the indiplon 20 mg group dropped out because of adverse events, compared with 6.4% of the indiplon 10 mg group, and 5.2% of the placebo group.

Baseline age, sex, and sleep characteristics were similar between the groups. Those receiving indiplon demonstrated significant improvement in sleep onset, sleep maintenance, and sleep duration measures on the first night. Global sleep improvement relative to placebo was demonstrated throughout the study period in the indiplon groups. Significantly more subjects on indiplon met ISI remission criteria compared with placebo. Indiplon-treated patients also reported improvement in insomnia-related daytime impairment (indexed using the three-item ISI impact factor).

Objective measures of daytime sleepiness were not assessed due to the short half-life of indiplon (1.5–2 h). The agent was associated with a mild "rebound" effect compared with placebo; on night two of the sudden withdrawal period, 1.1% of placebo subjects met rebound criteria compared with 11.1% of those who took indiplon 10 mg and 11.4% of those who took indiplon 20 mg. There appeared to be no benzodiazepine-like withdrawal symptoms as assessed by the BWSQ.

Side effects were transient, with the top five being headache, amnesia, dizziness, upper respiratory infection, and somnolence. The severity of adverse events did not seem to differ between the two doses of indiplon and placebo.

The authors conclude that subjectively reported measures of sleep onset, sleep maintenance, sleep duration, and overall quality of sleep were improved in subjects treated with indiplon compared with placebo, and that the treatment effect was demonstrable throughout the length of the study. Furthermore, adverse events were mild-to-moderate and transient, but they did note an incremental increase in the incidence of adverse events with the higher dose (20 mg) of indiplon.

The authors note several limitations to their study. The data were subjective and did not include polysomnography (or actigraphy) findings, which limits the ability to comment definitively on "rebound" after drug discontinuation. Other limitations were the high drop-out rate (approximately 50%), the exclusion of those with comorbid illnesses (psychiatric and acute medical), and the lack of assessment of adherence to nightly dosing. This reviewer would add the further limitation of an absence of objective assessment of "residual" daytime sleepiness or neurocognitive dysfunction.

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A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia

Roth T, Seiden D, Wang-Weigand S et al.
Curr Med Res Opin 2007;**23**:1005–14.

Ramelteon is a novel treatment for insomnia that has demonstrated efficacy in younger adults. In this double-blind, placebo-controlled study, the investigators examined the efficacy and safety of ramelteon in older adults with chronic primary insomnia. The drug was found to reduce latency to persistent sleep and increase total sleep time, and no residual effects on cognitive or psychomotor performance were noted. It was well tolerated by most participants.

Ramelteon is a new medication for insomnia that targets MT_1 and MT_2 melatonin receptors, and has no documented abuse potential. In the present double-blind, placebo-controlled study, the authors investigated the safety and efficacy of the drug in older adults with chronic primary insomnia.

Overall, 100 individuals (63 women; mean age 71 years) participated in the study. Almost all participants (95%) were of Caucasian origin. Following two nights of polysomnography (PSG), each subject was randomized to receive ramelteon 4 mg, ramelteon 8 mg, and placebo, in one of six sequences. The administration phases of each agent were separated by washout periods. Each treatment condition lasted for two nights and included PSG. Next-day cognitive and psychomotor assessments and a sleep questionnaire were completed.

Compared with placebo, ramelteon 4 mg was associated with a 9.7-min reduction in latency to persistent sleep (LPS; $p<0.001$), a 9-min increase in total sleep time (TST) ($p<0.04$), and a 1.8% increase in sleep efficiency (SE; $p<0.04$), as measured using PSG. Ramelteon 8 mg produced a 7.6-min reduction in LPS ($p=0.005$), an 11.6-min increase in TST ($p=0.007$), and a 2.4% increase in SE ($p=0.007$), compared with placebo. The drug was observed to have minimal impact on the number of nighttime awakenings, and no statistically significant impact on wake after sleep onset. Small but significant drug effects were noted when considering sleep architecture. Regarding self-report measures, the sole statistically significant effect was a 10-min reduction in sleep latency with ramelteon 4 mg compared with placebo ($p=0.04$).

The investigators did not observe any effects of ramelteon on cognitive or psychomotor measures. However, the drug was associated with better scores for two items of a measure of emotion than placebo. One-quarter of the participants reported one or more adverse event (AE), and the highest incidence of AEs was recorded with the ramelteon 4-mg dose (14%, compared with 7% for ramelteon 8 mg, and 9% for placebo). Most AEs were mild or moderate, for example, headache or nausea. Only one AE, which was noted in the placebo condition, was rated as severe. There were no AEs rated as serious, and none that prompted the withdrawal of a participant from the study.

These findings demonstrate the efficacy of ramelteon in improving PSG-measured LPS, TST, and SE in older adults with chronic insomnia. There were no negative next-day residual effects and no serious AEs associated with the treatment. In conclusion, these results support the notion that the drug is efficacious in older adults with chronic insomnia, and suggest that it is tolerated well in this population.

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Acupuncture for insomnia

Cheuk DK, Yeung WF, Chung KF et al.
Cochrane Database Syst Rev 2007;(3):CD005472.

The authors of this systematic review investigated whether or not acupuncture and its variants are safe and effective treatments for insomnia. They determined that clinical heterogeneity precluded extensive meta-analysis, and that methodological problems render the evidence inadequate to support the use of these interventions for the treatment of insomnia.

To determine whether acupuncture and related therapies safely improve sleep, quality of life, and functioning in individuals with insomnia, the present authors systematically reviewed relevant randomized, controlled trials. They performed a search for studies that met the following criteria:

- Randomized allocation of treatment conditions.
- Compared the use of acupuncture (including acupressure, laser acupuncture, and electroacupuncture) with a control condition (including placebo, no treatment, or sham therapy).
- Parallel-group or crossover design.
- Single-blind, double-blind, or unblinded design.
- Included participants with insomnia, with the condition documented as "sleep difficulties" at the very least.

Of the 26 studies initially indentified by the search strategy, seven met the inclusion criteria. However, there was considerable clinical heterogeneity regarding the populations, participant ages, settings, interventions (e.g.

acupuncture alone, acupressure, auricular therapy, acupuncture plus estazolam, or transcutaneous electrical acupoint stimulation [TEAS]), types of control condition (e.g. no treatment, sham treatment, placebo, sleep hygiene advice, or medication), and durations of follow-up (between 3 and 12 weeks) in the selected trials. Methodological quality was generally judged as "poor."

The results of an individual study that compared acupressure with "no treatment" suggest that sleep quality score improved more in those who were treated than in those who were not (standardized mean difference [SMD] –2.49, 95% confidence interval [CI] –3.20 to –1.78) [1]. Pooled results from similar studies suggested that post-treatment sleep quality was better in those who received treatment than in those who did not (SMD –0.55, 95% CI –0.89 to –0.21) [2,3]. Similarly, the results of a study comparing acupuncture with placebo suggest that acupuncture produced more favorable sleep quality scores (SMD –1.08, 95% CI –1.86 to –0.31) [4], and a group comparing TEAS with "no treatment" observed a better post-treatment sleep quality score in those receiving TEAS (SMD –0.74, 95% CI –1.22 to –0.26) [3].

However, meta-analysis of three studies of acupuncture that had the subjective report of sleep quality as an outcome indicated that acupuncture was no more likely to yield improvements than control conditions (relative risk 1.66, 95% CI 0.68–4.03) [1,5,6].

There was only one adverse event in the seven studies reviewed, providing preliminary evidence that this class of intervention is reasonably safe.

The present authors conclude that methodological problems are likely to have biased the results of the included trials. Furthermore, the combined evidence of the few randomized, controlled trials of these procedures is not adequate to support the use of acupuncture for treating insomnia. This article highlights the fact that research in this area is at a very early stage of development. Therefore, the results of large, high-quality studies that further investigate the use of acupuncture in insomnia are eagerly awaited.

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SLEEP-DISORDERED BREATHING

Sexual function and obstructive sleep apnea–hypopnea: a randomized clinical trial evaluating the effects of oral-appliance and continuous positive airway pressure therapy

Hoekema A, Stel AL, Stegenga B et al.
J Sex Med 2007;**4**:1153–62.

Sexual dysfunction commonly occurs in men with obstructive sleep apnea–hypopnea syndrome (OSA). The authors of this article compared sexual function in men who had OSA with that of men in whom OSA was not assessed, and investigated whether or not treatment of the syndrome was associated with improved sexual functioning. Following treatment, improvements were observed in indices of OSA but not in sexual function.

Sexual dysfunction is common in men with obstructive sleep apnea–hypopnea syndrome (OSA). In the present study, the investigators compared sexual function in men who had OSA with that of control participants. They also examined whether or not treatment with oral appliances or continuous positive airway pressure (CPAP) was associated with changes in sexual function in men with OSA, using an unblinded, randomized study design.

Participants with OSA were males aged >20 years (mean age 49±9 years) with an apnea–hypopnea index (AHI) ≥5 events/h, measured using polysomnography (PSG). They were required to have no history of prior apnea treatment, to be in a heterosexual relationship, and to be free of potentially confounding medical or dental conditions and medications. The control participants were age-matched men without sexual complaints, in whom OSA was not tested for.

At baseline, all participants completed the Golombok Rust Inventory of Sexual Satisfaction (GRISS). Men with OSA also completed the Epworth Sleepiness Scale (ESS), had their testosterone levels measured, and were assigned either an oral appliance that repositioned the mandible (n=20) or CPAP (n=27), by block randomization. Overall, 14 participants in the oral appliance group and 24 in the CPAP group completed both baseline and follow-up measures (PSG, ESS, and GRISS).

Those with OSA had higher baseline levels of erectile dysfunction (p=0.01) and sexual dissatisfaction (p=0.03) than the control participants. After treatment with oral appliances (median duration 82 days) and CPAP (median duration 76 days), there were improvements in OSA measures, but no significant improvements in sexual

function or testosterone levels. Baseline erectile dysfunction severity was negatively correlated with improved erectile function after treatment ($p<0.001$).

In conclusion, the investigators observed higher levels of sexual dysfunction in men with OSA than in control participants. Methodological problems, including a failure to test for OSA in the "control" group, a small sample size, and important baseline differences between treatment groups, preclude interpretations concerning the potential efficacy of oral appliances or CPAP to improve sexual function.

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C-reactive protein, obstructive sleep apnea, and cognitive dysfunction in school-aged children

Gozal D, Crabtree VM, Sans Capdevila O et al.
Am J Respir Crit Care Med 2007;**176**:188–93.

In the current study, the investigators examined the relationships between obstructive sleep apnea (OSA), cognitive dysfunction, and C-reactive protein (CRP) levels in children. They observed that children with OSA were more likely to exhibit cognitive dysfunction than their counterparts who do not snore, or who snore habitually but do not have OSA. Furthermore, those with OSA had significantly higher levels of high-sensitivity CRP.

The findings of a number of prior studies have established a relationship between sleep-disordered breathing (SDB) and cognitive dysfunction [1]. The authors of the current study have previously reported that levels of C-reactive protein (CRP) decrease in children when they are treated for SDB [2]. In this article, they report on an assessment of the role of CRP in children with SDB, some of whom had cognitive dysfunction, and some of whom did not.

Prior to the administration of cognitive tests, polysomnographic recordings were collected for 278 children aged 5–7 years. From these data, obstructive apnea–hypopnea indexes were calculated. Cognitive assessment instruments included the Differential Ability Scales and the Neuro-Psychological Assessment Battery. High-sensitivity CRP (hsCRP) measurements were also obtained during the study.

The results showed that children with OSA were more likely to achieve lower scores for global cognitive function than those who did not snore, or those who were habitual snorers without OSA ($p<0.0001$). When hsCRP levels were compared, no significant differences were observed between habitual snorers without OSA and non-snoring children; however, a significantly higher concentration was observed in those with OSA compared with both non-snoring children and habitual snorers without OSA. The findings also demonstrated that not all children who exhibited SDB had a decrease in cognitive performance; this suggests that other factors, such as the environment or possible genetic susceptibility, have a role.

In summary, the investigators of this study examined the complex relationship between hsCRP levels, neurocognitive defects, and SDB in children. The findings of previous studies have also demonstrated that children with OSA exhibit decreases in the ratio of the neuronal metabolites *N*-acetylaspartate and choline in the left hippocampus and right frontal cortex [3]. Thus, these pathways and their relationships with both environmental and genetic factors should be explored in more depth.

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Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome

Kono M, Tatsumi K, Saibara T et al.
Chest 2007;**131**:1387–92.

Metabolic syndrome is characterized by a clustering of medical conditions (including visceral obesity, dyslipidemia, and hypertension) that are common among individuals with obstructive sleep apnea (OSA). To explore whether OSA might have a role in the pathogenesis of metabolic syndrome, the authors of this preliminary study compared the prevalence of the conditions comprising metabolic syndrome in non-obese men with and without OSA.

Obstructive sleep apnea (OSA) is often associated with dyslipidemia, hypertension, hyperglycemia, and obesity. Similarly, metabolic syndrome is characterized by visceral obesity in combination with at least two additional factors from a range including dyslipidemia, hypertension, and hyperglycemia or insulin resistance.

In this cross-sectional study, the investigators explored the possibility that OSA plays a part in the development of metabolic syndrome, by examining the prevalence of dyslipidemia, hypertension, and hyperglycemia in non-obese men with and without OSA.

Participants with a body mass index (BMI) of ≤30 kg/m^2 were selected from 1205 consecutive male Japanese patients

with complaints of snoring, daytime sleepiness, or both. The investigators completed polysomnography (PSG) tests, radiological measurements of visceral fat accumulation (VFA), and other assessments. Participants were divided into two groups on the basis of their apnea–hypopnea index (AHI): those with OSA (AHI ≥5 events/h), and those without OSA (AHI <5 events/h). Patients in the two groups were matched by age, VFA, and BMI. This yielded 42 participants with OSA and 52 without the condition.

It was found that those with OSA, compared with those without the syndrome, had higher mean systolic blood pressure (131±3 mmHg vs. 125±1 mmHg, respectively; $p<0.05$) and fasting plasma glucose levels (111±6 mg/dL vs. 93±3 mg/dL; $p<0.05$), and were more insulin resistant (scores using the homeostasis model assessment method: 3.7±0.4 vs. 2.5±0.2; $p<0.05$). Furthermore, a higher proportion of participants with OSA had hypertension (45.2% vs. 15.4%; $p<0.01$), dyslipidemia (47.6% vs. 25.0%; $p<0.05$), and hyperglycemia (33.3% vs. 9.6%; $p<0.01$). Of those with OSA, 19% had two or more metabolic abnormalities (i.e. combinations of hypertension, hyperglycemia, or dyslipidemia), compared with 3.8% of those without OSA ($p<0.05$). AHI was a significant predictor of the number of such abnormalities in regression analysis ($p<0.05$), but BMI and arterial oxygen saturation were not.

The finding of a higher prevalence of metabolic abnormalities in non-obese men with OSA than in those without the syndrome suggests that affected individuals may be at an elevated risk of developing metabolic syndrome. The limitations of this study include its cross-sectional design (which precludes any inferences about direction of potential causal associations), and its small, homogeneous sample.

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CLINICAL MANAGEMENT

Lack of perceived sleep improvement after 4-month structured exercise programs

Elavsky S, McAuley E.

Menopause 2007;**14**:535–40.

The findings of this study suggest that a 4-month program of yoga and moderate exercise does not improve subjective sleep quality in middle-aged women with vasomotor symptoms.

Previous studies demonstrate conflicting findings regarding the effects of exercise on sleep, although it has been suggested that exercise may increase the length of sleep, among other benefits [1]. The authors of the current article state that perimenopausal women are at risk of sleep difficulties and, as a result, are a good population in which to study the effects of exercise on sleep. They cite the results of a cross-sectional study of Italian menopausal women, which suggest that those who regularly exercised exhibited improved sleep [2]. The current study was designed to test the hypothesis that a 4-month program of walking (moderate-intensity exercise) and yoga (low-intensity exercise) in middle-aged, inactive women would improve their sleep quality. In addition, the investigators aimed to examine changes in depression and menopausal symptoms on sleep quality independent of exercise.

In all, 164 sedentary or low-activity, middle-aged women with vasomotor symptoms were recruited from media advertisements. Quality of sleep was assessed with the Pittsburgh Sleep Quality Index; menopausal symptoms were measured using the Greene Climacteric Scale; depressive symptoms were investigated with the Beck Depression Inventory; and physical activity (that outside the intervention) levels were recorded by the Aerobics Center Longitudinal Study Physical Activity Survey. Subjects were randomly assigned to either a wait-list control group or 4-month walking or yoga groups. The walking group met three times a week for 1 h, as did the participants in the yoga group. The questionnaires were administered at the start and end of the program in the intervention and control groups.

The findings demonstrated no significant intervention effects regarding total sleep quality, although the walking group demonstrated a trend towards a small improvement. When the authors examined factors outside of the program (depression, menopausal symptoms, and exercise), only alterations in menopausal symptoms correlated with changes in sleep quality.

The authors conclude that their results did not demonstrate improvements in subjective sleep quality using 4 months of a walking or yoga program in middle-aged women. However, they note that the study was limited by a lack of objective measures of sleep and that the statistical power was low.

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Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness

Fava M, Thase ME, Debattista C et al.
Ann Clin Psychiatry 2007;**19**:153–9.

When depressive symptoms persist despite treatment for major depressive disorder, patients have been shown to be at a greater risk of relapse. The authors of the current study investigated the use of modafinil, a wake-promoting agent, in combination with selective serotonin reuptake inhibitor therapy in patients who were partial responders to treatment with antidepressants and who had residual fatigue and sleepiness.

The *Diagnostic and Statistical Manual of Mental Disorders* criteria for the diagnosis of major depressive disorder (MDD) include sleep difficulty. Residual symptoms following treatment of MDD have been linked to a higher rate of depressive relapse [1]. The aim of the current study was to evaluate the combined use of modafinil and selective serotonin reuptake inhibitor (SSRI) therapy in depressed patients with residual fatigue and sleepiness symptoms following antidepressant therapy.

A retrospective, pooled analysis of two double-blind, placebo-controlled studies [2,3] of modafinil and SSRI therapy in patients with MDD was performed. Depression rating and severity, sleepiness, and fatigue were evaluated throughout the studies.

The present investigators observed that sleepiness and Clinical Global Impression – Improvement scores were significantly more favorable in the modafinil-plus-SSRI group at week 1 and at the final visit (as late as week 6 in one of the studies and week 8 in the other), compared with the group receiving placebo plus an SSRI. Statistically significant differences were not observed between the two groups for comparisons at time points during weeks 2–8. Between-group fatigue severity scores were significantly different only at week 1, with reduced fatigue noted for the combination therapy group. Compared with those receiving placebo, results obtained using the Hamilton Depression Rating Scale were significantly improved for the group receiving modafinil on weeks 1, 3, 6, and at the final visit. The most common adverse event in both groups was headache.

These findings suggest that modafinil is a safe, effective choice for add-on therapy in patients with MDD who exhibit fatigue and sleepiness as persistent complaints with SSRI treatment; however, the drug is not currently licensed for this indication. Furthermore, the results stress the importance of treating sleep difficulties separately from depression. Additional studies should be performed to assess the use of multiple therapies in treating depression and sleep difficulties independently.

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Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice

Espie CA, MacMahon KM, Kelly HL et al.
Sleep 2007;**30**:574–84.

Group cognitive–behavioral therapy for insomnia (CBT-I) administered by trained nurses out-performed "treatment as usual" in this community, general medicine-based randomized trial. However, the effect sizes were smaller than those observed in previously conducted efficacy studies of CBT-I.

Chronic insomnia is widely prevalent in general practice patients and while treatment with pharmacological agents, such as benzodiazepine receptor agonists, is effective in acute insomnia, few long-term efficacy studies have been performed [1]. Cognitive–behavioral therapy for insomnia (CBT-I) has been demonstrated as being efficacious in primary insomnia [2] but it is labor intensive and, as the present authors point out, it is not known whether it is clinically feasible to provide CBT-I in the primary care setting.

Patients with chronic insomnia (diagnosed according to guidance from the *International Classification of Sleep Disorders – Revised* and the *Diagnostic and Statistical Manual of Mental Disorders*, along with standard quantitative criteria) were identified from visits to general practitioners or from sleep medication prescription records, and were randomized to CBT-I or "treatment as usual" (TAU). Data were collected at various time points from a wide variety of self-reported measures and sleep diaries, and actigraphy was also performed.

CBT-I consisted of weekly, 1-h sessions in groups of four to six participants, and were facilitated by a trained nurse. A series of five sessions was completed. Of the 201 eligible patients, 107 were allocated to CBT-I and 94 to TAU. In the CBT-I group, 76 patients completed the full course of therapy, 19 were lost to follow-up, and the remainder

completed some of the therapy. Of the TAU group, 67 completed follow-up, 16 were lost to follow-up, and the remainder did not receive the allocated intervention.

After treatment, percentage improvements in self-reported measures of sleep favored the CBT-I group over the TAU group; however, some loss of the effect of CBT-I was noted at 6-month follow-up. Improvements in actigraphy measures were significantly greater for wake time after sleep onset with CBT-I compared with TAU.

The authors conclude that nurse-administered, small-group CBT-I is a feasible and promising "first-line" insomnia intervention in general practice.

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NARCOLEPSY

Amygdala dysfunction in narcolepsy-cataplexy

Khatami R, Birkmann S, Bassetti CL.
J Sleep Res 2007;**16**:226–9.

Khatami et al. carried out the present study to explore the neurophysiological mechanisms that might explain the pathological link between emotion and motor function in cataplexy. The acoustic startle reflex was utilized as a measure of the association between emotion and motor function. The authors observed that narcolepsy patients failed to exhibit startle potentiation when subjected to unpleasant stimuli, and conclude that their findings reflect narcoleptic dysfunction in the amygdala.

A core feature of narcolepsy is cataplexy, the sudden onset of muscular paralysis triggered by strong emotion. Given that cataplexy is considered unique to narcolepsy, there is good reason to investigate the mechanisms which underlie it, as the findings may help in elucidating the pathophysiology of this sleep disorder. Khatami et al. aimed to explore the neurophysiological mechanisms that might explain the pathological link between emotion and motor function in episodes of cataplexy in eight patients with narcolepsy and eight age- and gender-matched controls.

Their study employed the acoustic startle reflex (ASR) to assay the link between emotion and motor function. Subjects were shown either unpleasant, neutral, or pleasant/humorous pictures, and approximately 3–5 s afterwards received a 50-ms burst of white noise in order to elicit the startle response. This response was measured using electromyographic recordings from a series of muscle groups.

The authors observed a normal ASR in narcolepsy patients; however, these individuals did not exhibit startle potentiation when subjected to unpleasant stimuli. While this study incorporated only a small sample, and thus the significance of the findings is unclear, the investigators conclude that the data reflect a dysfunction in the amygdala in narcolepsy. The results of further studies will be needed to determine if this is indeed the case.

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MOVEMENT DISORDERS

Burden of restless legs syndrome on health-related quality of life

Kushida C, Martin M, Nikam P et al.
Qual Life Res 2007;**16**:617–24.

Comparing Short Form-36 survey scores from patients with restless legs syndrome and adjusted population norms, the authors of this article conclude that patients with the condition have unique self-assessed mental and health decrements in quality of life.

Restless legs syndrome (RLS) is characterized by an urge to move the extremities that is usually worse during periods of rest or inactivity. The condition demonstrates a circadian propensity to worsen shortly before sleep. The urge to move is experienced as being unpleasant (e.g. "creeping," "crawling," "burning," or "throbbing") and temporarily improves with movement. RLS is more common in women, the elderly, and in those with iron deficiency, Parkinson disease, or chronic renal failure. The authors of the current study investigated the unique health burdens on quality of life (QOL) associated with RLS.

Nationwide telephone sampling of US adults was used to identify recruits with RLS. The random sampling strategy, which included one participant per household, yielded a sample that matched the population proportions of the four US Census regions. Participants were ≥18 years old and met RLS screening criteria if they reported experiencing all of four symptoms occurring at least 2 days or nights per week and being at least moderately distressing.

The Short Form-36 (SF-36) Health Survey was administered to 187 study participants identified from 5964 individuals

screened (prevalence rate 3.1%), of whom 158 provided responses. Responses to the items of the SF-36 are aggregated into eight health subscales (mental health, role emotional, social functioning, vitality, general health, body pain, role physical, and physical functioning) and into two component scales (physical and mental).

The SF-36 scores were compared with norms from patient and general populations in the US, including the 1998 US general population and those with type 2 diabetes, depression, and obstructive sleep apnea (OSA). Comorbid conditions (obesity, asthma, chronic pulmonary disease, epilepsy, folate deficiency, rheumatoid arthritis, and hypertension) were controlled for so that the unique QOL burden of RLS could be estimated.

The majority of those with RLS were women (63%); the average age was 53.25 years; and >40% were severely distressed by the symptoms. Health-related QOL (HRQOL) was significantly lower for those with RLS compared with normative values on all scales and subscales of the SF-36. The greatest differences in means were found in the physical functioning and general health subscales.

These effects on HRQOL remained substantial when the burden of RLS was compared with that of type 2 diabetes, depression, and OSA. The HRQOL scores of the RLS sample were similar to those of patients with OSA. The HRQOL burden of RLS remained when adjusted for the presence of comorbid conditions. The authors conclude that the unique health burdens experienced by patients with RLS are greater than previously suspected.

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EPIDEMIOLOGY

Sleep problems in primary care: a North Carolina family practice research network (NC-FP-RN) study

Alattar M, Harrington JJ, Mitchell CM et al.

J Am Board Fam Med 2007;**20**:365–74.

In this study, the investigators used a questionnaire to assess the prevalence and correlates – both demographic and medical – of sleep-related disturbances in adult patients in the primary care setting. They observed a high prevalence of disturbances, with sleepiness during activities, "dozing off" during activities, and maintenance insomnia being particularly common.

The authors of this article aimed to increase our understanding of the prevalence and correlates of sleep disturbances in the primary care population. They examined questionnaire data from 1934 adult primary care patients from five family practice offices; overall, 68% of the sample was female, and the mean age was 50±18 years. Regarding ethnic origin, 58% of the participants were white, 30% were African American, and 9% were Latin American.

More than half of the participants (55%) reported daytime sleepiness, and 37% reported "dozing off" during activities at least once per week. Symptoms of restless legs syndrome (RLS) were reported at least once per week by 28% of the sample. One-third of the subjects (33%) reported snoring loudly at least once per week, while 14% reported stopping breathing or gasping during sleep at the same frequency. Maintenance insomnia, defined as waking three or more times during the night, was noted by 34% of the respondents.

Participants aged ≥65 years were more likely than adults aged <65 years to doze off during activities (odds ratio [OR] 1.4; p≤0.001; 95% confidence intervals are not provided by the authors). However, surprisingly, the older participants were less likely to report awakening three or more times per night (OR 0.79; p≤0.05), gasping for breath (OR 0.58; p≤0.01), or snoring (OR 0.74; p≤0.05) than their younger counterparts.

In relation to men, women had a lower likelihood of gasping for breath (OR 0.69; p≤0.01) and of snoring (OR 0.54; p≤0.001). Compared with white participants, those of Latin American origin were less likely to report daytime sleepiness (OR 0.53; p≤0.001), dozing off (OR 0.49; p≤0.001), RLS (OR 0.46; p≤0.001), and snoring (OR 0.53; p≤0.001). Whether or not a participant had received higher education was also found to be associated with a number of sleep-related symptoms; however, a discrepancy between the article's text and tables makes the direction of this correlation difficult to interpret.

In multivariate-adjusted regression analyses, numerous medical comorbidities were observed to be associated with sleep-related complaints. Pain, functional limitations, depression, and lower ratings of mental or physical health were most predictive of disturbances. Smoking, lung disease, and vascular disease (hypertension and heart disease) were also associated with sleep complaints.

In conclusion, the findings from the present study suggest that sleep complaints are common in primary care patients and are associated with age, ethnicity, education, gender, and health-related variables. Primary care physicians should screen for these sleep complaints, which can often result from or exacerbate medical comorbidities.

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worldsleep07: The 5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies

Cairns, QLD, Australia, September 2–6, 2007

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Apart from its setting in beautiful Cairns (QLD, Australia), and its varied social agenda, worldsleep07 was a truly memorable meeting because of the high quality of exciting research findings presented by a large group of international scientists in a comprehensive program.

Trainee day

The meeting began on September 2nd with a "trainee day" covering topics targeted at postgraduate students and early career researchers. The day started with an inspiring keynote address by Anna Wirz-Justice (Psychiatric University Clinic Basel, Basel, Switzerland) who highlighted, and possibly reminded attendees, that science is an activity that is "done among friends." The key message was that, although the way that science is "carried out" in the 21st Century differs to that in earlier times, with the sale of technical services and knowledge now becoming increasingly important, the core values (e.g. balance, curiosity, and determination) can still be applied to ensure sound scientific outcomes.

During the remainder of the first day, a variety of courses were available. These ranged from sessions in the traditional "Year-in-Review" series, which encompassed the latest basic, clinical, and human experimental research findings, to workshops examining ethical issues, or how to balance a science career with family life, for example. A number of the sleep field's experts were on hand to give practical advice.

Opening ceremony: the function of mammalian sleep

Beginning the entertaining opening ceremony, Jerome Siegel (University of California, Los Angeles, CA, USA) delivered the keynote address: "Clues to the functions of mammalian sleep" (see [1] for a related review). Appropriately, Professor Siegel began by discussing the sleep-related peculiarities of the monotremes, specifically the platypus and echidna, which were previously (and incorrectly) thought not to have a brain stem large enough for rapid eye movement (REM) sleep. The vast differences in the sleep architecture of other mammals, such as the bottlenose dolphin, killer whale, and fur seal, were then highlighted. Professor Siegel's "take-home" message was that the function of sleep, in particular REM sleep, is still, to a large extent, unknown. The mysteries of the purpose of sleep and the effects of sleep disruption were themes carried throughout the meeting. In a subsequent presentation, Professor Siegel additionally presented findings highlighting a correlation between the loss of hypothalamic hypocretin (also known as orexin) neurons (known to be important in the pathophysiology of narcolepsy) and the stages of Parkinson's disease [2].

Meeting highlights

Other interesting presentations at the meeting included those by Charles Czeisler (Brigham and Women's Hospital, Boston, MA, USA), David Dinges (University of Pennsylvania, Pennsylvania, PA, USA), Allan Pack (University of Pennsylvania), and Emmanuel Mignot (Stanford University, Stanford, CA, USA).

Dr Czeisler presented a highly informative and personal view of the impact of sleep loss on driving and physician performance (see [3–7] for related publications), describing the frustrations faced in attempts at changing public attitudes and shift-work patterns. He pleaded with sleep physicians to take leading roles in changing outdated policies (especially regarding those for trainee physicians) that, in his view, put lives at risk. He additionally highlighted the current challenges faced by sleep medicine professionals, such as reducing waiting times for the diagnosis of sleep-disordered breathing (SDB), implementing clinical standards

for diagnosis, developing innovative techniques to treat obstructive sleep apnea (OSA), and improving patient adherence to existing treatments. The overriding sentiment was that healthcare professionals must not be complacent regarding the hazards of sleep deprivation.

Professor Dinges, meanwhile, considered the important question: "How much sleep do we need?" He described the areas where more information is needed before this question can be answered. For example, one topic for further investigation is the issue of variable individual responses to sleep deprivation. Furthermore, Professor Dinges commented on the reliability of evidence available from population studies regarding the health consequences of sleep; several poster presentations at the meeting reported associations between sleep duration and health consequences, such as obesity and cardiovascular disease (e.g. [8]). These proposed relationships are "U-shaped" in adults, with both short and long sleep durations being associated with an increased risk of morbidity. He said that while the data from population studies are compelling, they provide only one "level" of evidence. Other evidence, such as that from randomized trials, is required before recommendations regarding the role of sleep in these outcomes are incorporated into public health strategies. Finally, he also identified that patient adherence to continuous positive airway pressure treatment is an important area for further clinical research [9].

A highly interesting and thought-provoking talk was given by Dr Pack, who paid tribute to Harvey Colten (Columbia University Medical Center, New York, NY, USA), who sadly died earlier in 2007. Dr Colten chaired the Committee on Sleep Medicine and Research that authored the recent report *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* [10]; Dr Pack praised the Institute of Medicine (Washington, DC, USA) for their involvement in the publication.

In his talk, he predicted that in the future, medicine will be "personalized;" meaning that preventive measures and treatments will be specific to individuals based on their genetic and biological profiles. In addition, Dr Pack spoke of his vision for a multidisciplinary approach to sleep research within major academic centers [11]. In his opinion, the threats to this include university administrators not sharing this vision, a lack of investment in sleep research by funding bodies, and an insufficient number of young researchers [12]. Moreover, the increasing number of pulmonologists within the sleep field could be detrimental to future research requiring individuals with a strong neuroscience background, he opined. He also expressed concern that the insistence on using polysomnography (PSG) as the major investigative tool in clinical sleep medicine may be misguided.

In a separate session, Dr Mignot presented data from the Stanford School of Medicine's Center for Narcolepsy. He highlighted that while there is a close association between narcolepsy and the human leukocyte antigen (HLA)-DQB1*0602 genotype, suggestive of an autoimmune etiology, the exact nature of this relationship is still unclear. Indeed, a panel discussion at the meeting emphasized the frustrated attempts to characterize the autoimmune origin of the condition [13]. Dr Mignot spoke about his recent experiences with the Wisconsin Sleep Cohort Study, in which a significant proportion of the general population, and in particular, those with the HLA status observed in narcolepsy, exhibited markedly short sleep latencies in the Multiple Sleep Latency Test (MSLT) [14]. Describing a remarkable array of genetic manipulation studies, he reported on the use of the zebrafish as a model for understanding sleep physiology, sleep disorders, and sleep pharmacology (see [15]).

Meeting themes

The worldsleep07 program was organized into a number of specialized themes, including neuropharmacology/endocrinology, sleep biology, clinical sleep medicine, sleep and breathing, behavioral sleep medicine, and sleep in children. The highlights from some of these topics are presented below.

Sleep in children

There is concerning emerging evidence that children with SDB, and specifically OSA, may be at an increased risk of hypertension and cardiovascular complications. For example, in a study using continuous blood pressure measurement, Denise O'Driscoll (Monash University, Melbourne, VIC, Australia) examined cardiovascular response after spontaneous arousal in healthy children and during obstructive respiratory events in children with SDB undergoing an overnight PSG test. Compared with the healthy control group, children with SDB were found to have larger "surges" in mean arterial pressure and heart rate, which were strongly influenced by arousal type. These responses are similar to those observed in adults, suggesting that cardiovascular surges in children with OSA may contribute to increased hypertension and cardiovascular complications.

Raouf Amin (Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA) reported that children with SDB have greater blood-pressure variability in response to respiratory events compared with those without the condition. However, in a study in which children with SDB were matched with control subjects, and those with comorbidities were excluded, he observed that children with SDB did not exhibit a greater prevalence of pulmonary hypertension than their control counterparts.

David Gozal (University of Louisville, Louisville, KY, USA) outlined his previous and recent studies examining OSA in childhood. He suggested that hypoxia secondary to OSA is associated with inflammatory changes that predispose children to develop cardiovascular disease, independently of body weight. In a discussion on inflammatory markers of OSA, he proposed a triple-risk, OSA morbidity model, which implies an interaction between the environment, OSA severity, and individual susceptibility to cardiovascular disease. He said that when taken together, these findings argue for the inclusion of measurements of subcortical arousal, continuous blood pressure, and heart-rate variability in PSG montages for children with suspected SDB.

For some time, there has been an understanding that SDB in children can result in deficits in neurocognition [16]. What is still unknown, however, is whether or not these deficits are permanent. Declan Kennedy (University of Adelaide and Women's and Children's Hospital, Adelaide, SA, Australia) presented the results of a study in which children with SDB underwent overnight PSG and neurocognitive testing prior to, and 6 months after, adenotonsillectomy (believed by many to "cure" SDB in children). These children were age- and gender-matched with non-snoring, healthy control subjects. The results showed that while sleep and externalizing behavior improved in the children with SDB, some aspects of neurocognitive functioning were still impaired 6 months after surgery, when compared with control participants. Although this implies that the neurocognitive deficits associated with SDB may be permanent, Dr Kennedy concluded with the suggestion that a longer follow-up period is required before any substantive claims can be made. Furthermore, as Louise O'Brien (University of Michigan, Ann Arbor, MI, USA) argued in a review of this area, the causal relationship between SDB and neurobehavioral dysfunction has yet to be clarified. While the results of many studies have exhibited a relationship between SDB and deficits in neurocognition, there are just as many trials with inconsistent findings and unexpected results across the neurobehavioral domains [17]. As an example, Dr O'Brien discussed how hyperactivity appears to be more common in children with mild SDB than severe SDB [17]. This, along with the emerging evidence of the relationship between SDB and inflammatory markers, indicates that data from birth-cohort studies are needed to gain a full understanding of the developmental context of SDB.

Sleep biology

A recently emerging area of interest is that of between-individual differences in susceptibility to the effects of sleep deprivation. With implications regarding fatigue in driving and shift work, questions have been asked as to why some people appear particularly susceptible, while others are more resilient. Sean Drummond (University of California, San Diego, CA, USA) reported the results of a recent study examining inter-individual differences in working memory in young adults (aged 19–39 years) following 42 hours of total sleep deprivation (TSD). It was found that individuals were uniquely resilient or vulnerable to TSD in specific components of working memory; that is, a person may have shown significant deficits in rehearsal span and episodic memory, but exhibited no change in attention, for example. Interestingly, in a similar experiment with older adults (aged 60–82 years), between-individual differences were observed for attention and rehearsal span, but not episodic memory.

Just as there is variation in susceptibility to sleep deprivation, between-individual differences have also been exhibited regarding sensitivity to countermeasures for fatigue or sleepiness, such as caffeine. Hans-Peter Landolt (University of Zürich, Zürich, Switzerland) used a randomized, placebo-controlled design to study the effects of caffeine on sleep propensity and performance in caffeine-sensitive and caffeine-insensitive men. The results of this study demonstrated a reduction in theta power, enhanced performance on a random number generation task, and improved sustained attention in psychomotor vigilance testing in caffeine-sensitive subjects only. It is clear from findings such as these that future fatigue research, such as that related to drowsy driving and the consequences of shift-work, need to consider between-individual differences.

Neuropharmacology/endocrinology

The meeting featured a wealth of presentations examining the sleep–endocrine interface. In two sessions, the speakers focused on the associations between sleep and gonadal hormones, including the relationships between OSA, low testosterone levels, and erectile dysfunction. The links between age-related alterations in sleep and hormone secretion were also highlighted. Another sitting was devoted to considering the interaction between sleep and the hypothalamic–pituitary–adrenal stress axis. Assimilating the findings discussed in these presentations, the bi-directionality of the interactions between sleep and the secretion of various hormones was clearly evident (see [18] for a related review).

Interest in the function of slow-wave sleep (SWS) and slow-wave activity (SWA) has stimulated research in a number of different areas. Derk-Jan Dijk (University of Surrey, Guildford, UK) suggested that, based on evidence regarding the neurocognitive effects of SWS deprivation, slow waves may be regulated homeostatically. In his study, disruption of SWS resulted in both subjective and objective daytime sleepiness effects, with significant increases in

scores recorded on the Karolinska Sleepiness Scale and in sleep propensity, as measured using the MSLT. In addition, SWS deprivation caused errors of commission, attention-modulated motion sensitivity, and motor tracking, but it had no effect on working memory. Interestingly, it was found that for performance tests in which the results did not respond to SWS disruption, there was a response to TSD, suggesting a homeostatic mechanism.

Eve van Cauter (University of Chicago, Chicago, IL, USA) argued that one of the most important functions of SWS is to regulate endocrine and metabolic function. The results of a study on the relationship between SWA and glucose metabolism showed that an increase in the former led to an amplified release of insulin. The investigators estimated that 50–70% of the body's response to glucose could be predicted by SWA levels.

Furthermore, SWS reduction has been associated with a decrease in glucose tolerance, creating important implications for the management of diabetes. Giulio Tononi (University of Wisconsin–Madison, Madison, WI, USA) highlighted that the function of SWS may be to ensure synaptic homeostasis. He provided results from a series of neuroimaging studies demonstrating that slow waves are traveling waves with a distinct origin and direction of propagation, and that disruption of SWS may suppress some slow waves but leave others intact. Using internal capsule stroke models, Dr Tononi showed that traveling slow waves avoid dysfunctional cortical areas, which suggests that the brain must be fully functional in order to propagate slow waves, thus supporting a role for sleep at the cellular level. The disparities presented in each of these studies highlight that the function of SWS requires further extensive research.

The hypocretin system and pharmacotherapy: new developments

The hypothalamic hypocretin system is a major stabilizer of wakefulness, and was reviewed at this meeting by Clifford Saper (Harvard Medical School, Boston, MA, USA), who also presented data from his laboratory describing the potential hypothalamic circuitry mediating the food-entrainable oscillator (see [19,20] for related publications). The hypocretin system, which has a key role in narcolepsy, comprises neurons releasing two peptides, hypocretins 1 and 2 (orexins A and B), which act at hypocretin receptors 1 and 2 [13]. It has been shown that patients with narcolepsy–cataplexy have undetectable cerebrospinal fluid hypocretin-1 levels [21]. It would be expected that hypocretin receptor antagonists could prove to be effective hypnotics [22], but because ineffective hypocretin neurotransmission in narcolepsy also results in cataplexy, such agents may cause the latter as a major side effect. The orally active agent ACT-078573 is an antagonist at both hypocretin receptors [23], and preliminary data were presented at the meeting regarding its use in 39 patients with primary insomnia. At a dose of 400 mg, the drug resulted in shorter sleep latency and reduced wake after sleep onset compared with placebo. Data from larger studies will be necessary to fully assess the clinical utility of the compound, including those investigating the possibility for cataplexy with prolonged use.

Disclosures

S Biggs is supported by the MS McLeod Foundation. S Taheri has no relevant financial relationships to disclose.

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