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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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Contents

LEADING ARTICLE

Sex Differences in Sleep and Sleep Disorders: A Focus on Women's Sleep

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The effect of gender/sex[1] on normal sleep and on the prevalence, presentation, and course of a variety of sleep disorders is a contemporary area of scientific inquiry. Men and women can differ in the presentation and course of several sleep disorders. Insomnia and restless legs syndrome (RLS) are more prevalent in women and sleep-disordered breathing (SDB), narcolepsy, and rapid eye movement sleep behavior disorder are more prevalent in men. This manuscript briefly discusses the current knowledge concerning sex differences in sleep, and then focuses on sleep across a woman's life cycle, including the menstrual cycle, pregnancy, *post partum*, menopause transition, and post-menopause. The differences between self-reported sleep and polysomnographically defined sleep parameters are highlighted, along with issues arising in women's sleep at different stages of their reproductive cycles. This review underlines the need to consider stages of the reproductive cycle when evaluating and treating women for insomnia, SDB, and RLS. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(4):125–33.

Women have a greater need for sleep than men [1], and report spending more time in bed [2]. Sex differences in sleep need and sleep time persist even after adjusting for comorbid psychiatric disorders in adults and in adolescents [2,3]. As depicted in Figure 1, women also report more sleep problems and poorer sleep quality than men in nearly all age groups [2,4,5], and have an increased risk of suffering insomnia (risk ratio 1.41) across different age groups, which is most pronounced among the elderly [6]. Paradoxically, polysomnographic (PSG) recordings indicate that men may have a more disturbed, lighter sleep [7,8], and show a faster age-related decline in slow wave sleep (SWS) than is seen in women [9], although a differential influence of sex on the impact of aging, as analyzed by power spectral density during non-rapid eye movement (NREM) sleep over a wide frequency range (0.25–25.0 Hz), has not been shown [10]. Women have higher absolute slow wave activity (SWA) in NREM sleep [11–13], implying a deeper sleep than that of men. However, when SWA in NREM sleep is normalized relative to SWA in REM sleep, women have lower relative SWA than men, consistent with their subjective complaints of lighter sleep [12]. Further investigation into sex differences in subjective and objective sleep assessments is required to improve understanding of this issue.

The higher incidence of sleep problems in women may be partly attributed to their increased risk for the development of psychiatric disorders that are associated with sleep disturbances, such as depression. Interestingly, alterations in sleep architecture associated with major depressive disorder (MDD) are sex-dependent, starting in adolescence [14]. Depressed men are more likely to have a deficiency in SWS whereas depressed women show a tendency towards ultradian rhythm abnormalities (low temporal coherence) compared with healthy controls [15,16]. Taken together, these results provide some support for a sex-dependent pathophysiology of MDD [16].

As is the case for insomnia, the prevalence of restless legs syndrome (RLS) is higher in women than in men (approximately two-fold) [17,18]; however, there are few sex differences in the clinical presentation of RLS, based on self-reports [19]. In contrast, emerging data suggest sex differences in some physiological markers of RLS, such as changes in heart rate following a leg movement in periodic limb movement disorder (PLMD) [20] and in levels of cerebrospinal fluid ferritin [21]. There are no known sex differences in the prevalence of PLMD [22].

Obstructive sleep apnea (OSA) is more common in men, with the male-to-female ratio reported as being between 2:1

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1. Throughout the article we use the term sex rather than gender. The term sex is commonly used as a biological category of male or female and the term gender is most often used in reference to social or cultural categories (The American Heritage® book of English usage [digital]: a practical and authoritative guide to contemporary English.1996; Available from: Bartleby.com).

Figure 1. Age and sex distribution of patients with severe insomnia.

Adapted with permission from [160].

and 4:1 [23–27]. As reviewed by Kapsimalis and Kryger [27], biological sex differences in OSA can be explained by several mechanisms, including obesity pattern and fat distribution, upper airway anatomy and function, the control of breathing, and hormone status. Sleep-disordered breathing (SDB) in women varies according to reproductive status, with higher levels seen in post-menopausal women [26,28,29]. It is believed that gonadal hormones play a role in the regulation of breathing during sleep, as discussed later in this manuscript.

Narcolepsy is also more prevalent in men than in women, with an estimated incidence rate of 1.72 cases per 100 000 persons per year for men and 1.05 cases for women [30]; however, the reason for this difference is not known. Sex differences do not appear to be present for NREM parasomnias [31] or delayed sleep phase insomnia [32]; however, for unknown reasons, REM sleep behavior disorder (RSBD) occurs almost exclusively in men [33].

Sleep in women across the reproductive cycle

The menstrual cycle

The ovulatory menstrual cycle is characterized by a regulated variation in reproductive hormones across a 25–35 day period. The follicular phase lasts from the first day of menses until ovulation, which occurs around day 14. The luteal phase refers to the second half of the menstrual cycle when progesterone, being produced from the corpus luteum, predominates. The marked variation in hormones across the menstrual cycle influences not only reproductive tissue function but also other processes such as sleep.

Surveys and studies based on subjective reports have found that women across a wide age range (aged 18–50 years) report more sleep disturbances during the premenstrual week and during the first few days of menstruation than at other times [34–36]. The SWAN (Study of Women's Health Across the Nation), which included 630 women in their late reproductive stage or entering the menopausal transition, also showed that trouble sleeping varied with cycle phase, being more likely to occur during the early follicular and late luteal phases of the menstrual cycle [37]. There is therefore strong evidence that women perceive the quality of their sleep as poorer around the time of menstruation.

However, studies using PSG have shown that sleep continuity, sleep efficiency, SWS, and SWA during NREM sleep remain stable across the ovulatory menstrual cycle in young, healthy women [38–40]. On the other hand, REM sleep and spindle activity are affected by menstrual cycle phase. REM sleep has an earlier onset [41,42], and there are small decreases in the percentage of REM sleep during the luteal phase [38,43–45], which may be related to the rise in body temperature since REM sleep is sensitive to temperature variations [46]. Electroencephalogram (EEG) activity in the frequency range of sleep spindles is significantly increased during the luteal phase compared with other phases of the menstrual cycle [38,39], possibly representing an interaction between endogenous progesterone metabolites and γ-aminobutyric acid$_A$ (GABA$_A$) membrane receptors [38].

To summarize, with the exception of REM sleep and spindle activity, sleep-stage distribution is stable across the normal menstrual cycle despite substantial changes in the hormonal milieu. Additional research is therefore needed to understand the documented increase in self-reported sleep disturbances at the beginning or end of the menstrual cycle.

Oral contraceptives

Oral contraceptives suppress endogenous reproductive hormones, preventing ovulation; hence, the women taking them do not have normal menstrual cycles. They do not appear to influence subjective sleep quality [47], but do alter sleep architecture. Women taking oral contraceptives have less SWS [47–50], more Stage 2 sleep [47], a shorter REM onset latency, and more REM sleep [49], compared with women with natural menstrual cycles. Exogenous steroid hormones therefore appear to exert a different influence on sleep than endogenous progesterone and estrogen.

Menstrual cycle-associated sleep disorders

Two sleep disorders that are temporally related to the menses have been proposed in the International Classification of

Sleep Disorders – premenstrual insomnia and premenstrual hypersomnia [51]. A third category, premenstrual parasomnia (sleep behavior disorder), has been suggested by Schenck and Mahowald [52], who cited two cases of premenstrual sleep terrors and injurious sleep-walking.

Women with premenstrual insomnia complain of insomnia only during the premenstrual phase of the menstrual cycle. The cause of premenstrual insomnia is unknown, but there is some evidence from a case study that desynchronization of temperature and sleep–wake rhythms in the luteal phase could be a contributing factor [53].

Premenstrual hypersomnia is a rare sleep disorder characterized by excessive sleepiness that typically begins a few days before menstruation onset and ends a few days after [51]. Few cases have been published, and most of the patients have had unremarkable hormonal changes accompanying their symptoms [54,55]. Oral contraceptives have been successfully used to treat this condition [54,56]. Further study of women with menstrual cycle-associated sleep disorders is indicated to establish the etiology.

Sleep in women with menstrual cycle disorders

Menstrual cycle-related complaints, including mood disorders, pain associated with menstruation, and endocrinological problems such as polycystic ovary syndrome, are common in women. Women who suffer from a menstrual cycle-associated disorder may experience concomitant changes in their sleep.

Premenstrual syndrome and premenstrual dysphoric disorder

Up to 70% of women of reproductive age suffer from premenstrual syndrome (PMS) and 3–8% report disabling premenstrual symptoms such as depressed mood, irritability, and anxiety that qualify them for a diagnosis of premenstrual dysphoric disorder (PMDD) [57,58]. Women with PMS typically report sleep-related complaints associated with their PMS symptoms such as hypersomnia, insomnia, fatigue, sleep perturbation by body movements and awakenings, and disturbing dreams [59].

PSG studies of women with PMS or PMDD have reported inconsistent results [41,59–62]. Two studies of women with severe PMS [41] or PMDD [60] found a greater percentage of Stage 2 sleep as well as either less SWS [41] or less REM sleep [60] compared with controls, but subsequent studies did not replicate these findings [61,62]. It is possible there is variation within the population of women with PMDD, such that altered sleep is only apparent in some women. More studies are needed to better understand the role of sleep in PMS or PMDD, particularly in light of findings that total and partial sleep deprivation may improve mood [63].

Primary dysmenorrhea

Primary dysmenorrhea refers to painful menstruation that occurs in the absence of visible pelvic pathology in as many as 50% of young women [64]. The painful menstrual cramps experienced by these women every cycle significantly impact productivity and quality of life [64], and disturb sleep both subjectively and objectively (lower sleep efficiency, increased time spent awake, moving, and in Stage 1 light sleep, and less REM sleep) compared with pain-free phases of the menstrual cycle, and compared with women who don't suffer menstrual pain [43]. Disturbed sleep, in turn, may further exacerbate pain, as sleep deprivation is associated with a decreased pain threshold [65]. Treatment of nocturnal pain with analgesics should alleviate painful cramps and consequently improve sleep quality in women with dysmenorrhea.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) affects 4–12% of women of reproductive age [66]. Women with PCOS typically present with irregular or absent cycles, androgen excess (evident as hirsutism), and bilateral polycystic ovaries [67]. Insulin resistance is also an important component of PCOS [67], and obesity occurs in approximately 50% of cases [68]. The combination of obesity, excess androgen production, and insulin resistance places women with PCOS at an increased risk for SDB. The prevalence and severity of SDB in women with PCOS are much higher than in age- and weight-matched controls [69–71]. Women with PCOS should be evaluated for SDB and treated appropriately, not only to improve alertness but also to address potential insulin resistance, which is common in both disorders [70]. Indeed, glucose tolerance and SDB may be influenced by a common mechanism in PCOS [70]. Given that, in women, upper airway resistance is lower during the luteal phase when progesterone is high compared with the follicular phase [72], and that SDB is more severe in the follicular phase than in the luteal phase in women with OSA [73], menstrual cycle phase should be considered when evaluating SDB in women with PCOS.

Pregnancy

Sleep during pregnancy varies across trimesters as hormonal and physical changes take place. Pregnant women commonly report sleep disruption due to nausea, backache, frequent urination, heartburn, leg cramps, and shortness of breath, especially in the first and third trimesters [74]. Both longitudinal and cross-sectional PSG studies have also indicated an increase in wake after sleep onset in pregnant women, particularly in the third trimester [45,75–77]. Findings regarding changes in total sleep time and amounts

of REM sleep and SWS are mixed, although most studies have found that compared with age-matched controls, and within subjects earlier in pregnancy and the *post partum* period, the third trimester is associated with decreased percentages of REM sleep [73–75] and SWS [45,77,79–83], an overall decrease in EEG power density [76], increased prevalence of alpha-delta sleep [82], and increased percentage time spent in Stage 1 light sleep [75–77,84]. Both hormonal (prolactin and progesterone) and physical changes associated with pregnancy contribute to the documented decrease in sleep continuity, particularly in the third trimester (see [85] for a review). Altered respiration, esophageal reflux, heartburn, leg cramps, leg pain, back pain, and increased fetal movement can all disturb sleep [77,86,87]. Interestingly, despite the ubiquitous nature of frequent night waking during the latter part of pregnancy, less than 20% of individuals viewed their awakenings as problematic [45]. The impact of poor sleep during pregnancy on ease of delivery is not clear. One study found no significant correlations between the length of labor and maternal self-reported sleep quality during the day or the week preceding labor [88]; however, another reported that women in their first pregnancy who were awake >15% of time after sleep onset during the ninth month of pregnancy (based on actigraphy) had longer labors and a greater incidence of cesarean deliveries [89].

Sleep disorders during pregnancy

Data on the prevalence of psychophysiological insomnia during pregnancy and on the effects of pregnancy in women who experienced insomnia prior to pregnancy are lacking. Pregnancy is associated with an increased risk for two other sleep disorders, SDB and RLS. Although epidemiological data on the prevalence of SDB during pregnancy is absent, survey-based studies indicate that the incidence of snoring is higher for pregnant women during the second half of pregnancy (12–23%) than for age-matched non-pregnant controls (approximately 4%) [90–92], and symptoms of SDB, including snoring, choking, and apneic events, increase as pregnancy progresses [93]. Sleep apneic events during late pregnancy are associated with marked blood pressure fluctuations that remit post-natally, along with a reduction in number of arousals [94]. Women with pre-existing SDB and those at high risk for SDB should be carefully monitored during pregnancy as OSA could increase the risk of pre-eclampsia [95,96] and neonatal complications [97].

The incidence of RLS during pregnancy is 2–3 times greater than in the general population [98], with a much higher prevalence in women who do not take folate supplements (80%) [99]. Prospective studies find the incidence of RLS increases across the trimesters of pregnancy [75,100]. For most women, RLS emerges during pregnancy and remits following delivery, but may re-emerge during subsequent pregnancies [101]. Although there are no published estimates regarding the prevalence of PLMs during pregnancy, the possibility that PLMD is present in pregnant women with RLS needs to be considered as the two disorders often co-occur [102].

Post partum

The first 6 months *post partum* are associated with a substantial increase in time awake after sleep onset and a decrease in sleep efficiency, relative to the last trimester of pregnancy [77,78,84,103–106]. However, this period is also associated with marked increases in SWS [83,84,107] and REM pressure [41], as evidenced by earlier REM onset, which normalizes by 3 months *post partum* [84,108]. These changes are commonly observed upon recovery from experimentally induced sleep disruption or sleep restriction [109,110].

Sleep continuity gradually improves 3–12 months *post partum* [111], a process that is closely tied to the sleep patterns and mode of feeding the infant. Breastfeeding mothers report more night awakenings (especially when sleeping with their infants [108]) and more fatigue than non-breastfeeding mothers, but similar total nocturnal sleep time compared with mothers who are not breastfeeding [112,113]. There is evidence that maternal self-reported sleep quality is determined by the number of awakenings rather than the total time awake attending to the baby [114].

As would be expected, maternal sleep fragmentation leads to increased self-reported daytime sleepiness and to negative mood [115–117], and may contribute to the development of *post partum* depression [118]. Interventions to improve an infant's sleep, and consequently the mother's, lead to an improvement in maternal mood [118–121]. Although these data might suggest a causal link between infant sleep and maternal depression, it is also possible that maternal depressive symptoms contribute to the severity of infant sleep disturbance, as infants of depressed mothers may sleep poorly because they are distressed, not sufficiently active during the day, or receive insufficient environmental cues to entrain their circadian rhythms [122]. It is also possible that the observed relationship between an infant's sleep and maternal depression reflects a reporting bias, as *post partum* women with current or past depression are awake during the night more than women without *post partum* depression [107], and may therefore be more aware of, and more likely to report, infant sleep disturbances.

Menopausal transition (perimenopause)

The menopausal transition refers to the period of time between the first onset of menstrual irregularity, or skipped

menses, and the final menstrual period [123]. The median age of onset of menstrual irregularity is 47 years, and the median age at final menstrual period is 51.4 years [123]. This transition period is marked by wide fluctuations in reproductive hormones as the number of ovarian follicles progressively declines and reaches a critical level.

Sleep difficulties increase as women enter the menopausal transition [29,37,124–130], even after adjustment for age and ethnicity [37]. In SWAN, the multi-ethnic, community-based cohort study of 3302 women, the likelihood of reporting sleeping difficulties was greater for women who were in early or late menopausal transition or who were post-menopausal, compared with premenopausal women [37,125]. A 10-year longitudinal study revealed that problems with sleeping, and secondarily vasomotor symptoms, were the most bothersome complaints associated with the transition to menopause [131]. An increase in self-reported perimenopausal sleep difficulties has been associated with vasomotor symptoms such as hot flashes [125], hormone levels [37], and psychological factors or mood [37,127,132]. In their review of the literature, Schmidt concluded that perimenopause, but not post-menopause, is associated with an increase in depressive symptoms [133]. However, although depressive illnesses are often associated with an increase in sleep disturbance, the direction of causality still needs to be determined. Interestingly, Kravitz et al. found that pregnanediol glucuronide, a progesterone metabolite, was significantly associated with an increase in trouble sleeping across the menstrual cycle in perimenopausal women but not in premenopausal women [37], suggesting a link between the hormonal changes of the menopausal transition and self-reported sleep difficulties.

PSG studies have shown little evidence of disturbed sleep in perimenopausal women. Whereas one study found that sleep stability tended to be lower in peri- and post-menopausal women than in premenopausal women, particularly in those women reporting hot flashes [134], the Wisconsin Sleep Cohort Study, the largest study to date measuring sleep physiologically in this group of women, reached a different conclusion [130]. After adjustment for confounding factors such as age, body mass index (BMI), and exercise, menopausal status was associated with self-reported sleep dissatisfaction but not with objectively measured sleep quality [130]. Moreover, sleep quality did not differ between women who did or did not report hot flashes during sleep [29,130].

Post-menopause

Post-menopause begins at the time of the last menstrual period, although it is only recognized after 12 months of amenorrhea [135]. Population-based surveys have found evidence for a link between menopause and self-reported sleep difficulties even after controlling for age and depression scores [130]. Odds ratios for comparisons of sleep difficulties between pre- and post-menopausal women range from 1.3–3.4 [125,126,130]. The increase in sleep difficulty and dissatisfaction with sleep in post-menopausal women appears to be primarily due to difficulty maintaining sleep, as reported by 35–60% of post-menopausal women [135].

In contrast, when sleep was objectively measured with PSG in pre- and post-menopausal women, "the proportion of time spent in the various sleep stages showed no indication of less-favorable sleep architecture" for post-menopausal women [29,130]. In fact, in this large population-based study, post-menopausal women had significantly better objectively defined sleep quality (3.4% more time spent in SWS, 13.4 min longer total sleep time, and a lower proportion of time spent awake) than premenopausal women. A smaller study of women without sleep complaints also found no evidence for poorer sleep quality in post- compared with premenopausal women [136].

Longitudinal studies may help clarify how sleep changes across the menopausal transition and during post-menopause. Future studies should include spectral analysis of the EEG, measurements of body temperature, autonomic nervous system responses, respiratory parameters, and repeated hormone measurements [137].

Relation of sleep continuity disturbance to hot flashes

Some studies have shown that vasomotor symptoms correlate strongly with both subjective and objective sleep disturbance [138–140]. However, studies that have tried to ascertain what proportion of awakenings result from hot flashes compared with the proportion that occur when flashes are absent have yielded inconsistent results. Our ability to perceive and report phenomena that occur during sleep is limited; hence, studies that use objective measures of sleep and hot flashes provide the most reliable data to answer this question. A recent study that used such measures suggested that the link between hot flashes and awakenings is not as strong as was previously believed [141]. This study of post-menopausal women found that "of awakenings occurring within 2 min of a hot flash, 55.2% occurred before, 40.0% after, and 5.0% simultaneously"[141]. In other words, the proportions of arousals and awakenings that occur shortly after a hot flash, and were therefore presumably "caused" by it, were similar to the proportions that occurred before a hot flash. On the other hand, a study of sleep in breast cancer survivors that

also used objective measures of sleep and hot flashes found that the 10-min periods around hot flashes included significantly more wake time and more stage changes to lighter sleep than other 10-min periods during the night [142]. Together, these findings indicate that the association between nocturnal hot flashes and awakenings might be mediated by another, as yet unidentified, common pathway.

Prospective outcome studies evaluating the efficacy of interventions that target hot flashes do not always find an association between reductions in nocturnal hot flash severity and clinically meaningful improvements in sleep [e.g. 143,144]. Available data on the impact on sleep of treatments for menopausal symptoms are inconclusive, and not all studies of hormone replacement therapy (HRT) have found beneficial effects on subjective or objective measures of sleep continuity (for a review, see Dzaja et al. [145]). Although the Women's Health Initiative study found a significant improvement in self-reported sleep quality after 1 year of HRT, the difference was considered small and clinically insignificant, and was not present at the 3-year follow-up [144]. Alternatives to HRT also differ in their impact on sleep. For example, some antidepressant medications can reduce hot flash severity, but their impact on sleep is variable. Mirtazapine has shown efficacy for hot flashes, though only in an uncontrolled study, and might be considered to treat patients with hot flashes and sleep disturbances [146].

Factors other than unstable hormone levels and vasomotor symptoms may contribute to the disruption of sleep or to the perceived poor sleep quality in post-menopausal women. Psychosocial factors post-menopausal women may face, such as adjustment to role transition as children leave the home or aging parents become frailer [147], as well as changes in health and sleep regulation systems (such as impaired photic input) [148], have been implicated in the etiology of sleep continuity disturbances. The relative contributions of these factors have not been systematically investigated. In addition, for post-menopausal women whose insomnia was triggered by symptoms associated with the transition to menopause, such as vasomotor disturbances, insomnia may persist even after these symptoms abate due to the development of conditioned insomnia. For example, a woman experiencing insomnia may lie in bed worrying about sleeping and, with time, lying in bed can become a cue for hyperarousal, which interferes with sleep. Thus, increased sleep effort and experience-associated hyperarousal may prolong insomnia even when menopausal symptoms diminish. Future studies investigating sleep in women during menopause should therefore include psychological measurements of hyperarousal and distorted cognitions.

Sleep-disordered breathing during menopause

Even after controlling for age and BMI, the prevalence of SDB increases with menopause [26,30,31]. The severity of SDB in post-menopausal women is not related to the severity of vasomotor symptoms or to circulating estradiol levels [149]; however, the incidence of SDB is lower in women receiving HRT [28,29,150]. Estrogen therapy can also reduce respiratory disturbance in post-menopausal women [151].

The increased incidence of SDB in post-menopausal women is thought to be related to an increase in abdominal fat distribution [152] and a decline in progesterone [27]. Progesterone increases the ventilatory response to hypercapnia and hypoxia [153–156] and may increase activity of the upper-airway dilator muscles [157], protecting premenopausal women from developing OSA. Indeed, when hypocapnia was experimentally induced during NREM sleep in pre- and post-menopausal women and in men, the change in the end-tidal CO_2 at the apnea threshold was highest in the premenopausal women, with no difference between post-menopausal women and men [158]. The study also found that HRT increased the change in end-tidal CO_2 at the apnea threshold. Although HRT might reduce SDB severity in post-menopausal women, fewer women are willing to take HRT since the publication of the results from the Women Health Initiative study [159]. Continuous positive airway pressure remains the most effective treatment of SDB in both men and women.

Summary

Sex is a relevant factor in the presentation and course of several sleep disorders, with insomnia and RLS being more prevalent in women and SDB, RSBD, and narcolepsy being more prevalent in men. Different stages in the reproductive life cycle of women (menstrual cycle, pregnancy, *post partum*, menopause transition, and post-menopause) are associated with unique factors that can contribute to increased prevalence and/or severity of self-reported sleep difficulty, insomnia, SDB, and RLS. The treatment of sleep disorders in women should therefore be considered in the context of their reproductive cycle.

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References

1. Ferrara M, De Gennaro L. How much sleep do we need? *Sleep Med Rev* 2001;**5**:155–79.
2. Lindberg E, Janson C, Gislason T et al. Sleep disturbances in a young adult population: can gender differences be explained by differences in psychological status? *Sleep* 1997;**20**:381–7.
3. Johnson EO, Roth T, Schultz L et al. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. *Pediatrics* 2006;**117**:e247–56.

4. Groeger JA, Zijlstra FR, Dijk DJ. Sleep quantity, sleep difficulties and their perceived consequences in a representative sample of some 2000 British adults. *J Sleep Res* 2004;**13**:359–71.
5. Middelkoop HA, Smilde-van den Doel DA, Neven AK et al. Subjective sleep characteristics of 1,485 males and females aged 50–93: effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol A Biol Sci Med Sci* 1996;**51**:M108–15.
6. Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep* 2006;**29**:85–93.
7. Bixler EO, Kales A, Jacoby JA et al. Nocturnal sleep and wakefulness: effects of age and sex in normal sleepers. *Int J Neurosci* 1984;**23**:33–42.
8. Williams RL, Karacan I, Hursch CJ. *Electroencephalography (EEG) of Human Sleep: Clinical Applications*. New York, John Wiley, 1974.
9. Ehlers CL, Kupfer DJ. Slow-wave sleep: do young adult men and women age differently? *J Sleep Res* 1997;**6**:211–5.
10. Carrier J, Land S, Buysse DJ et al. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology* 2001;**38**:232–4.
11. Dijk DJ, Beersma DGM, Bloem GM. Sex differences in the sleep EEG of young adults: visual scoring and spectral analysis. *Sleep* 1989;**12**:500–7.
12. Latta F, Leproult R, Tasali E et al. Sex differences in delta and alpha EEG activities in healthy older adults. *Sleep* 2005;**28**:1525–34.
13. Armitage R. The distribution of EEG frequencies in REM and NREM sleep stages in healthy young adults. *Sleep* 1995;**18**:334–41.
14. Robert JJ, Hoffmann RF, Emslie GJ et al. Sex and age differences in sleep macroarchitecture in childhood and adolescent depression. *Sleep* 2006;**29**:351–8.
15. Armitage R, Hoffmann R, Fitch T et al. Temporal characteristics of delta activity during NREM sleep in depressed outpatients and healthy adults: group and sex effects. *Sleep* 2000;**23**:607–17.
16. Armitage R, Hoffmann R, Trivedi M et al. Slow-wave activity in NREM sleep: sex and age effects in depressed outpatients and healthy controls. *Psychiatry Res* 2000;**95**:201–13.
17. Tison F, Crochard A, Leger D et al. Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT Study. *Neurology* 2005;**65**:239–46.
18. Hogl B, Kiechl S, Willeit J et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. *Neurology* 2005;**64**:1920–4.
19. Bentley AJ, Rosman KD, Mitchell D. Gender differences in the presentation of subjects with restless legs syndrome. *Sleep Med* 2006;**7**:37–41.
20. Gosselin N, Lanfranchi P, Michaud M et al. Age and gender effects on heart rate activation associated with periodic leg movements in patients with restless legs syndrome. *Clin Neurophysiol* 2003;**114**:2188–95.
21. Earley CJ, Connor JR, Beard JL et al. Ferritin levels in the cerebrospinal fluid and restless legs syndrome: effects of different clinical phenotypes. *Sleep* 2005;**28**:1069–75.
22. ASD Association. *The International Classification of Sleep Disorders: Diagnostic and Coding Manual, Revised*. Rochester MN, American Sleep Disorders Association, 1997.
23. Young T, Palta M, Dempsey J et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;**328**:1230–5.
24. Redline S, Kump K, Tishler PV et al. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med* 1994;**149**:722–6.
25. Kripke DF, Ancoli-Israel S, Klauber MR et al. Prevalence of sleep-disordered breathing in ages 40–64 years: a population-based survey. *Sleep* 1997;**20**:65–76.
26. Bixler EO, Vgontzas AN, Lin HM et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;**163**:608–13.
27. Kapsimalis F, Kryger MH. Gender and obstructive sleep apnea syndrome, part 2: mechanisms. *Sleep* 2002;**25**:499–506.
28. Polo-Kantola P, Erkkola R, Helenius H et al. When does estrogen replacement therapy improve sleep quality? *Am J Obstet Gynecol* 1998;**178**:1002–9.
29. Young T, Finn L, Austin D at al. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2003;**167**:1181–5.
30. Silber MH, Krahn LE, Olson EJ et al. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. *Sleep* 2002;**25**:197–202.
31. Ohayon MM, Guilleminault C, Priest RG. Night terrors, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. *J Clin Psychiatry* 1999;**60**:268–76.
32. Kamei Y, Urata J, Uchiyaya M et al. Clinical characteristics of circadian rhythm sleep disorders. *Psychiatry Clin Neurosci* 1998;**52**:234–5.
33. Dzaja A, Arber S, Hislop J et al. Women's sleep in health and disease. *J Psychiatr Res* 2005;**39**:55–76.
34. Manber R, Bootzin RR. Sleep and the menstrual cycle. *Health Psychol* 1997;**16**:209–14.
35. Baker FC, Driver HS. Self-reported sleep across the menstrual cycle in young, healthy women. *J Psychosom Res* 2004;**56**:239–43.
36. National Science Foundation. Women and Sleep Poll 1998 [cited 2006 March 13]; Available from: http://web.archive.org/web/20040608054453/ www.sleepfoundation.org/publications/1998womenpoll.cfm
37. Kravitz HM, Janssen I, Santoro N et al. Relationship of day-to-day reproductive hormone levels to sleep in midlife women. *Arch Intern Med* 2005;**165**:2370–6.
38. Driver HS, Dijk DJ, Werth E et al. Sleep and the sleep electroencephalogram across the menstrual cycle in young healthy women. *J Clin Endocrinol Metab* 1996;**81**:728–35.
39. Ishizuka Y, Pollak CP, Shirakawa S et al. Sleep spindle frequency changes during the menstrual cycle. *J Sleep Res* 1994;**3**:26–9.
40. Armitage R, Baker FC, Parry B. The menstrual cycle and circadian rhythms. In: Kryger M, Roth T, Dement W (eds). *Principles and Practice of Sleep Medicine* Philadelphia, Elsevier Saunders, 2005:1266–77.
41. Lee KA, Shaver JF, Giblin EC et al. Sleep patterns related to menstrual cycle phase and premenstrual affective symptoms. *Sleep* 1990;**13**:403–9.
42. Baker FC, Mitchell D, Driver HS. Sleep in the follicular and luteal phases of the menstrual cycle. *Actas de Fisiología* 2001;**7**:154.
43. Baker FC, Driver HS, Rogers GG et al. High nocturnal body temperatures and disturbed sleep in women with primary dysmenorrhea. *Am J Physiol* 1999;**277**:E1013–21.
44. Baker FC, Driver HS, Paiker J et al. Acetaminophen does not affect 24-h body temperature or sleep in the luteal phase of the menstrual cycle. *J Appl Physiol* 2002;**92**:1684–91.
45. Lee KA, McEnany G, Zaffke ME. REM sleep and mood state in childbearing women: sleepy or weepy? *Sleep* 2000;**23**:877–85.
46. Parmeggiani PL, Rabini C. Sleep and environmental temperature. *Arch Ital Biol* 1970;**108**:369–87.
47. Baker FC, Mitchell D, Driver HS. Oral contraceptives alter sleep and raise body temperature in young women. *Pflugers Arch* 2001;**442**:729–37.
48. Baker FC, Waner JI, Vieira EF et al. Sleep and 24 hour body temperatures: a comparison in young men, naturally cycling women and women taking hormonal contraceptives. *J Physiol* 2001;**530**:565–74.
49. Burdick RS, Hoffmann R, Armitage R. Short note: oral contraceptives and sleep in depressed and healthy women. *Sleep* 2002;**25**:347–9.
50. Henderson A, Nemes G, Gordon NB et al. Sleep of regularly menstruating women and of women taking an oral contraceptive. *Psychophysiology* 1970;**7**:337.
51. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Revised: Diagnostic and coding manual*. Chicago, American Academy of Sleep Medicine, 2001.
52. Schenck C, Mahowald M. Two cases of premenstrual sleep terrors and injurious sleep-walking. *J Psychosom Obstet Gynaecol* 1995;**16**:79–84.
53. Suzuki H, Uchiyama M, Shibui K et al. Long-term rectal temperature measurements in a patient with menstrual-associated sleep disorder. *Psychiatry Clin Neurosci* 2002;**56**:475–8.
54. Sachs C, Persson HE, Hagenfeldt K. Menstruation-related periodic hypersomnia: a case study with successful treatment. *Neurology* 1982;**32**:1376–9.
55. Billiard M, Guilleminault C, Dement WC. A menstruation-linked periodic hypersomnia. Kleine-Levin syndrome or new clinical entity? *Neurology* 1975;**25**:436–43.
56. Papy JJ, Conte-Devolx B, Sormani J et al. The periodic hypersomnia and megaphagia syndrome in a young female, correlated with menstrual cycle [author's transl]. *Rev Electroencephalogr Neurophysiol Clin* 1982;**12**:54–61.
57. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder – clinical procedures and research perspectives. *Gynecol Endocrinol* 2004;**19**:320–34.
58. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) 4th ed*. Washington, DC, American Psychiatric Association, 1994.
59. Mauri M. Sleep and the reproductive cycle: a review. *Health Care Women Int* 1990;**11**:409–21.
60. Parry B, Mendelson W, Duncan W et al. Longitudinal sleep EEG, temperature, and activity measurements across the menstrual cycle in patients with premenstrual depression and age matched controls. *Psychiatry Res* 1989;**30**:285–303.
61. Parry BL, Mostofi N, LeVeau B et al. Sleep EEG studies during early and late partial sleep deprivation in premenstrual dysphoric disorder and normal control subjects. *Psychiatry Res* 1999;**85**:127–43.
62. Chuong CJ, Kim SR, Taskin O et al. Sleep pattern changes in menstrual cycles of women with premenstrual syndrome: a preliminary study. *Am J Obstet Gynecol* 1997;**177**:554–8.
63. Parry BL, Cover H, Mostofi N et al. Early versus late partial sleep deprivation in patients with premenstrual dysphoric disorder and normal comparison subjects. *Am J Psychiatry* 1995;**152**:404–12.
64. Dawood MY. Dysmenorrhea. *Clin Obstet Gynecol* 1990;**33**:168–78.
65. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev* 2006;**10**:357–69.
66. Sheehan MT. Polycystic ovarian syndrome: diagnosis and management. *Clin Med Res* 2004;**2**:13–27.
67. Sartor BM, Dickey RP. Polycystic ovarian syndrome and the metabolic syndrome. *Am J Med Sci* 2005;**330**:336–42.
68. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;**18**:774–800.
69. Vgontzas AN, Legro RS, Bixler EO et al. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab* 2001;**86**:517–20.
70. Tasali E, Van Cauter E, Ehrmann DA. Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006;**91**:36–42.

71. Fogel RB, Malhotra A, Pillar G et al. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001;**86**:1175–80.
72. Driver HS, McLean H, Kumar DV et al. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. *Sleep* 2005;**28**:449–56.
73. Edwards N, Wilcox I, Sullivan C. Haemodynamic responses to obstructive sleep apnoeas in premenopausal women. *J Hypertens* 1999;**17**:603–10.
74. Wolfson A, Crowley, SJ, Anwer et al. Changes in sleep patterns and depressive symptoms in first-time mothers: last trimester to 1-year postpartum. *Behav Sleep Med* 2003;**1**:54–67.
75. Mindell JA, Jacobson BJ. Sleep disturbances during pregnancy. *J Obstet Gynecol Neonatal Nurs* 2000;**29**:590–7.
76. Brunner DP, Munch M, Biedermann K et al. Changes in sleep and sleep electroencephalogram during pregnancy. *Sleep* 1994;**17**:576–82.
77. Hertz G, Fast A, Feinsilver SH et al. Sleep in normal late pregnancy. *Sleep* 1992;**15**:246–51.
78. Driver HS, Shapiro CM. A longitudinal study of sleep stages in young women during pregnancy and postpartum. *Sleep* 1992;**15**:449–53.
79. Anders TF, Roffwarg HP. Relationship between infant and maternal sleep. *Psychophysiology* 1968;**5**:227–8.
80. Petre-Quadens O, De Barsy AM, Devos J et al. Sleep in pregnancy: evidence of foetal-sleep characteristics. *J Neurol Sci* 1967;**4**:600–5.
81. Hoppenbrowers T, Hodgman JE, Berntsen I et al. Sleep in women during the last trimester of pregnancy. *Sleep Res* 1979;**8**:150.
82. Schorr SJ, Chawla A, Devidas M et al. Sleep patterns in pregnancy: a longitudinal study of polysomnography recordings during pregnancy. *J Perinatol* 1998;**18**:427–30.
83. Karacan I, Heine W, Agnew HW et al. Characteristics of sleep patterns during late pregnancy and the postpartum periods. *Am J Obstet Gynecol* 1968;**101**:579–86.
84. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. *Obstet Gynecol* 2000;**95**:14–8.
85. Gaylor E, Manber R. Sleep and sleep disorders during pregnancy. In: Kushida C (ed). *Sleep Deprivation*: New York, Marcel Dekker Inc, 2003.
86. Baratte-Beebe KR, Lee K. Sources of midsleep awakenings in childbearing women. *Clin Nurs Res* 1999;**8**:386–97.
87. Worth J, Onyeije CI, Ferber A et al. The association between fetal and maternal sleep patterns in third-trimester pregnancies. *Am J Obstet Gynecol* 2002;**186**:924–5.
88. Evans ML, Dick MJ, Clark AS. Sleep during the week before labor: relationships to labor outcomes. *Clin Nurs Res* 1995;**4**:238–49.
89. Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. *Am J Obstet Gynecol* 2004;**191**:2041–6.
90. Guilleminault C, Querra-Salva M, Chowdhuri S et al. Normal pregnancy, daytime sleeping, snoring and blood pressure. *Sleep Med* 2000;**1**:289–97.
91. Loube DI, Poceta JS, Morales MC et al. Self-reported snoring in pregnancy: association with fetal outcome. *Chest* 1996;**109**:885–9.
92. Izci B, Vennelle M, Liston WA et al. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. *Eur Respir J* 2006;**27**:321–7.
93. Pien GW, Fife D, Pack AI et al. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep* 2005;**28**:1299–305.
94. Edwards N, Blyton DM, Hennessy A et al. Severity of sleep-disordered breathing improves following parturition. *Sleep* 2005;**28**:737–41.
95. Connolly G, Razak AR, Hayanga A et al. Inspiratory flow limitation during sleep in pre-eclampsia: comparison with normal pregnant and nonpregnant women. *Eur Respir J* 2001;**18**:672–6.
96. Edwards N, Blyton CM, Kesby GJ et al. Pre-eclampsia is associated with marked alterations in sleep architecture. *Sleep* 2000;**23**:619–25.
97. Franklin KA, Holmgren PA, Jonsson F et al. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Chest* 2000;**117**:137–41.
98. Manconi M, Govoni V, De Vito A et al. Pregnancy as a risk factor for restless legs syndrome. *Sleep Med* 2004;**5**:305–8.
99. Botez MI, Lambert B. Folate deficiency and restless-legs syndrome in pregnancy. *N Engl J Med* 1977;**297**:670.
100. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gend Based Med* 2001;**10**:335–41.
101. Goodman J, Brodie C, Ayida GA. Restless legs syndrome in pregnancy. *BMJ* 1988;**297**:1101–2.
102. Montplaisir J, Boucher S, Poirer G et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord* 1997;**12**:61–5.
103. Shinkoda H, Matsumoto K, Park YM. Changes in sleep-wake cycle during the period from late pregnancy to puerperium identified through the wrist actigraph and sleep logs. *Psychiatry Clin Neurosci* 1999;**53**:133–5.
104. Waters M, Lee KA. Differences between primigravidae and multigravidae mothers in sleep disturbances, fatigue, and functional status. *J Nurse Midwifery* 1996;**41**:364–7.
105. Kang MJ, Matsumoto K, Shinkoda H et al. Longitudinal study for sleep-wake behaviours of mothers from pre-partum to post-partum using actigraph and sleep logs. *Psychiatry Clin Neurosci* 2002;**56**:251–2.
106. Nishihara K, Horiuchi S. Changes in sleep patterns of young women from late pregnancy to postpartum: relationships to their infants' movements. *Percept Mot Skills* 1998;**87**:1043–56.
107. Coble P, Reynolds CF 3rd, Kupfer DH et al. Childbearing in women with and without a history of affective disorder. II. Electroencephalographic sleep. *Compr Psychiatry* 1994;**35**:215–24.
108. Mosko S, Richard C, McKenna J. Maternal sleep and arousals during bedsharing with infants. *Sleep* 1997;**20**:142–50.
109. Dement W, Greenberg S. Changes in total amount of stage four sleep as a function of partial sleep deprivation. *Electroencephalogr Clin Neurophysiol* 1966;**20**:523–6.
110. Tilley AJ, Wilkinson RT. The effects of a restricted sleep regime on the composition of sleep and on performance. *Psychophysiology* 1984;**21**:406–12.
111. Wolfson AR, Anwer U. Sleep and affect in pregnancy and postpartum months. Annual meeting of the Northeast Sleep Society, Worchester, MA, 2000.
112. Quillin SI. Infant and mother sleep patterns during 4th postpartum week. *Issues Compr Pediatr Nurs* 1997;**20**:115–23.
113. Elias MF, Nicolson NA, Bora C et al. Sleep/wake patterns of breast-fed infants in the first 2 years of life. *Pediatrics* 1986;**77**:322–9.
114. Packard AE, Martin-Okada R, Huang MI et al. Sleep disturbance and depression symptom severity in postpartum women. Associated Professional Sleep Societies meeting, Denver, CO, USA 2005.
115. Lee KA, DeJoseph JF. Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women. *Birth* 1992;**19**:208–13.
116. Troy NW. A comparison of fatigue and energy levels at 6 weeks and 14 to 19 months postpartum. *Clin Nurs Res* 1999;**8**:135–52.
117. Campbell I. Postpartum sleep patterns of mother-baby pairs. *Midwifery* 1986;**2**:193–201.
118. Hiscock H, Wake M. Infant sleep problems and postnatal depression: a community-based study. *Pediatrics* 2001;**107**:1317–22.
119. Armstrong KL, Van Haeringen AR, Dadds MR et al. Sleep deprivation or postnatal depression in later infancy: separating the chicken from the egg. *J Paediatr Child Health* 1998;**34**:260–2.
120. Leeson R, Barbour J, Romaniuk D et al. Management of infant sleep problems in a residential unit. *Child Care Health Dev* 1994;**20**:89–100.
121. Hiscock H, Wake M. Randomised controlled trial of behavioural infant sleep intervention to improve infant sleep and maternal mood. *BMJ* 2002;**324**:1062–5.
122. Field T. The effects of mother's physical and emotional unavailability on emotion regulation. *Monogr Soc Res Child Dev* 1994;**59**:208–27.
123. Santoro N. The menopausal transition. *Am J Med* 2005;**118**:S8–13.
124. Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. *Maturitas* 1998;**30**:41–50.
125. Kravitz HM, Ganz PA, Bromberger J et al. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. *Menopause* 2003;**10**:19–28.
126. Kuh DL, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. *Br J Obstet Gynaecol* 1997;**104**:923–33.
127. Baker A, Simpson S, Dawson D. Sleep disruption and mood changes associated with menopause. *J Psychosom Res* 1997;**43**:359–69.
128. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med* 2005;**118**:S14–24.
129. Shin C, Lee S, Lee T et al. Prevalence of insomnia and its relationship to menopausal status in middle-aged Korean women. *Psychiatry Clin Neurosci* 2005;**59**:395–402.
130. Young T, Rabago D, Zgierska A et al. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep* 2003;**26**:667–72.
131. Ford K, Sowers M, Crutchfield M et al. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. *Menopause* 2005;**12**:308–17.
132. Kloss JD, Tweedy K, Gilrain K. Psychological factors associated with sleep disturbance among perimenopausal women. *Behav Sleep Med* 2004;**2**:177–90.
133. Schmidt PJ. Mood, depression, and reproductive hormones in the menopausal transition. *Am J Med* 2005;**118**:5–8.
134. Shaver J, Giblin E, Lentz M et al. Sleep patterns and stability in perimenopausal women. *Sleep* 1988;**11**:556–61.
135. National Institutes of Health. State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med* 2005;**142**:1003–13.
136. Sharkey KM, Bearpark HM, Acebo C et al. Effects of menopausal status on sleep in midlife women. *Behav Sleep Med* 2003;**1**:69–80.
137. Polo O. Sleep in postmenopausal women: better sleep for less satisfaction. *Sleep* 2003;**26**:652–3.
138. Polo-Kantola P, Erkkola R, Irjala K et al. Climacteric symptoms and sleep quality. *Obstet Gynecol* 1999;**94**:219–24.

139. Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. *Sleep* 1994;**17**:497–501.
140. Erlik Y, Tataryn IV, Meldrum DR et al. Association of waking episodes with menopausal hot flushes. *JAMA* 1981;**245**:1741–4.
141. Freedman RR, Roehrs TA. Lack of sleep disturbance from menopausal hot flashes. *Fertil Steril* 2004;**82**:138–44.
142. Savard J, Davidson JR, Ivers H et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. *J Pain Symptom Manage* 2004;**27**:513–22.
143. Huang MI, Nir Y, Chen B et al. A randomized controlled pilot study of acupuncture for postmenopausal hot flashes: effect on nocturnal hot flashes and sleep quality. *Fertil Steril* 2006;**86**:700–10.
144. Hays J, Hunt JR, Hubbell FA et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol* 2003;**13**:S18–77.
145. Dzaja A, Arber S, Hislop J et al. Women's sleep in health and disease. *J Psychiatr Res* 2005;**39**:55–76.
146. Perez DG, Loprinzi CL, Barton DL et al. Pilot evaluation of mirtazapine for the treatment of hot flashes. *J Support Oncol* 2004;**2**:50–6.
147. Hislop J, Arber S. Sleep as a social act: a window on gender roles and relationships. In: Arber S, Davidson K Ginn J (eds). *Gender and Ageing: Changing Roles and Relationships* Maidenhead, Open University Press, 2003:186–205
148. Herljevic M, Middleton B, Thapan K et al. Light-induced melatonin suppression: age-related reduction in response to short wavelength light. *Exp Gerontol* 2005;**40**:237–42.
149. Polo-Kantola P, Saaresranta T, Polo O. Aetiology and treatment of sleep disturbances during perimenopause and postmenopause. *CNS Drugs* 2001;**15**:445–52.
150. Shahar E, Redline S, Young T et al. Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med* 2003;**167**:1186–92.
151. Manber R, Kuo TF, Cataldo N et al. The effects of hormone replacement therapy on sleep-disordered breathing in postmenopausal women: a pilot study. *Sleep* 2003;**26**:163–8.
152. Young T. Analytic epidemiology studies of sleep disordered breathing – what explains the gender difference in sleep disordered breathing? *Sleep* 1993;**16**:S1–2.
153. Hannhart B, Pickett CK, Moore LG. Effects of estrogen and progesterone on carotid body neural output responsiveness to hypoxia. *J Appl Physiol* 1990;**68**:1909–16.
154. Regensteiner JG, Woodard WD, Hagerman DD et al. Combined effects of female hormones and metabolic rate on ventilatory drives in women. *J Appl Physiol* 1989;**66**:808–13.
155. Zwillich CW, Natalino MR, Sutton FD et al. Effects of progesterone on chemosensitivity in normal men. *J Lab Clin Med* 1978;**92**:262–9.
156. Edwards N, Wilcox I, Polo OJ et al. Hypercapnic blood pressure response is greater during the luteal phase of the menstrual cycle. *J Appl Physiol* 1996;**81**:2142–6.
157. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. *J Appl Physiol* 1998;**84**:1055–62.
158. Rowley JA, Zhou XS, Diamond MP et al. The determinants of the apnea threshold during NREM sleep in normal subjects. *Sleep* 2006;**29**:95–103.
159. Roussouw JE, Anderson GL, Prentice PL et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.
160. Hohagen F, Rink K, Kappler C et al. Prevalence and treatment of insomnia in general practice. A longitudinal study. *Eur Arch Psychiatry Clin Neurosci* 1993;**242**:329–36.

LEADING ARTICLE

Excessive Sleepiness: Determinants, Outcomes, and Context

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

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Sleepiness level is determined by two interacting neurobiological processes: the homeostatic balance between sleep and wakefulness, and the endogenous circadian rhythm. Disruptions of these two processes contribute to excessive sleepiness in a variety of sleep disorders (e.g. insomnia, shift-work disorder) and in operational settings involving extended hours and shift work. However, excessive sleepiness manifests itself in diverse ways depending upon which variables are measured and how. Broadly, sleepiness measures can be categorized as subjective, physiological, or cognitive performance-related. Aside from a variety of technical measurement issues, different demand characteristics and other context parameters contribute to discrepancies between these categories in measured sleepiness. Diagnosing excessive sleepiness is complicated by the context-dependent diversity in outcomes and by the intertwined contributions of the underlying neurobiological processes. Therefore, for successful diagnosis and treatment of excessive sleepiness it is essential to consider the metrics used to assess it, the underlying neurobiology, and the context. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(4):134–40.

Neurobiological determinants of sleepiness

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

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

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

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Sleepiness due to sleep disorders

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

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

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

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

Sleepiness from occupational demands and lifestyle

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

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

Measuring sleepiness

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

Subjective sleepiness

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

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

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

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

Physiological sleepiness

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

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

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

Cognitive performance impairment

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

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

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

Discrepancies among measures of sleepiness and the role of context

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

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

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

Diagnosing excessive sleepiness

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

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

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

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

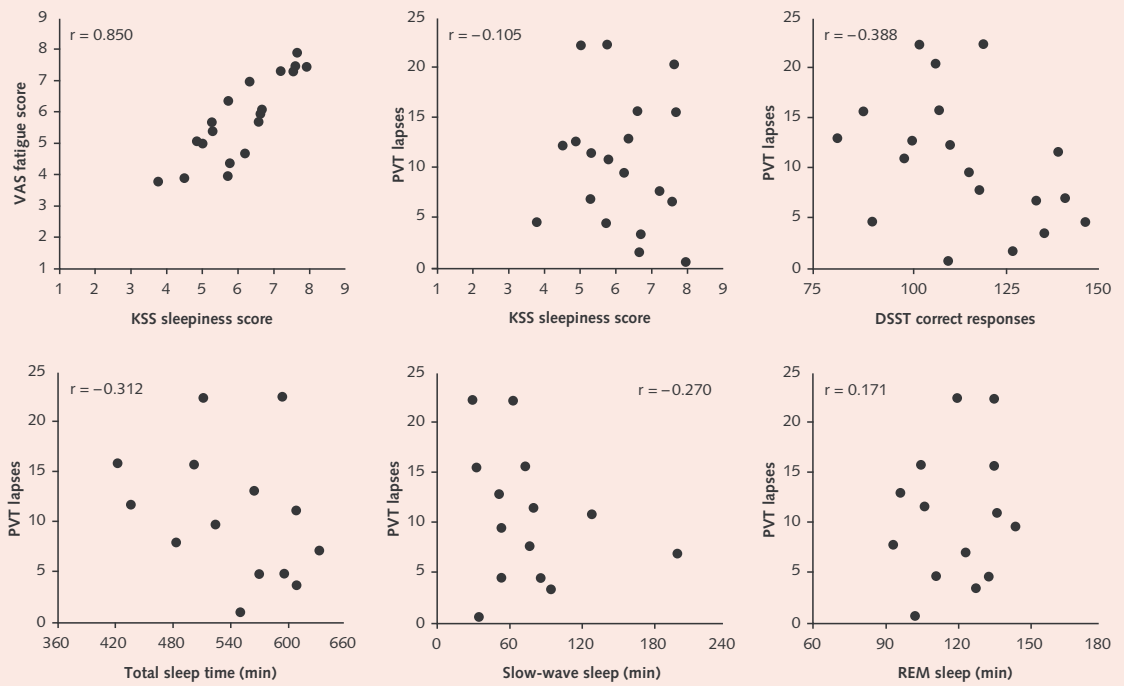
Treating excessive sleepiness

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

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

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

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

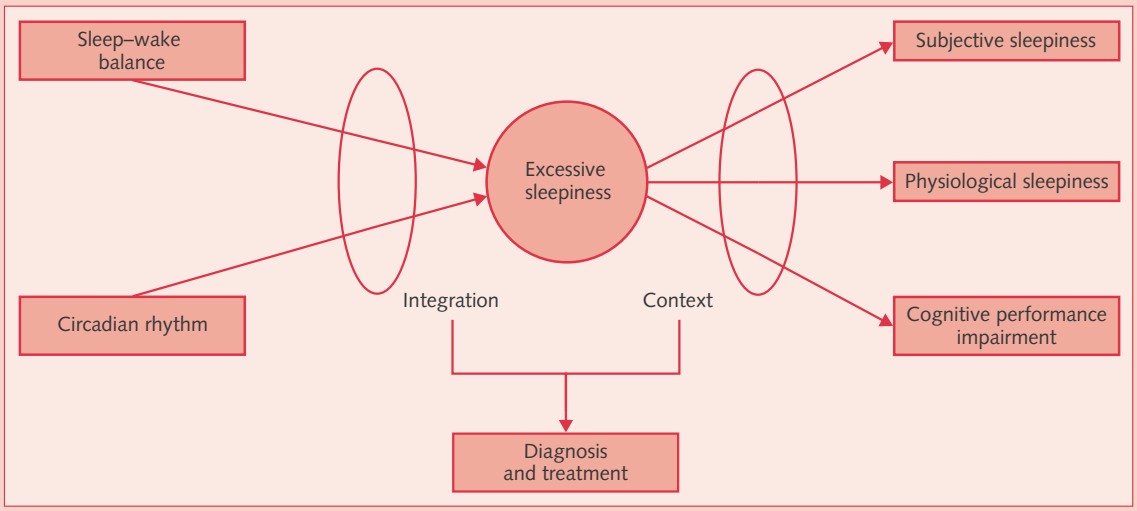


DSST: Digit–Symbol Substitution Task; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor Vigilance Test; REM: rapid eye movement; VAS: Visual Analogue Scale.

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

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

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



Conclusion

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

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References

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

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

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Sleep Disturbances and their Impact on Medical Disease and Morbidity

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Insomnia complaints are reported by nearly one-third of the general population; however, the diagnosis of insomnia is only made in 6–15%. Similarly, excessive daytime sleepiness is reported by approximately one in five people but only 2% of the general population is diagnosed with hypersomnia, narcolepsy, or behaviorally induced insufficient sleep syndrome. In the vast majority of individuals, sleep disturbances are caused by or are associated with various medical or neurological diseases, psychiatric disorders, or environmental factors. Therefore, it is imperative to diagnose these comorbid conditions prior to planning appropriate treatment. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(4):141–5.

Sleep disturbances encompass a broad range of phenomena, including insomnia, hypersomnia, sleep apnea, and restless legs syndrome (RLS). The latest edition of the *International Classification of Sleep Disorders* describes criteria for the diagnosis of >100 sleep disorders, divided into eight main categories [1]:

- Insomnias.
- Sleep-related breathing disorders.
- Hypersomnias of central origin.
- Circadian rhythm sleep disorders.
- Parasomnias.
- Sleep-related movement disorders.
- Isolated symptoms, apparently normal variants, and unresolved issues.
- Other sleep disorders.

Most sleep disorders are accompanied by insomnia, complaints of excessive daytime sleepiness (EDS), or both.

Insomnia

Insomnia symptoms are present in approximately 30% of the general population, but the diagnosis of insomnia is only made in 6–15% [2]. Therefore, it can be estimated that approximately 75 million people in the US and 150 million in Europe are affected by insomnia.

Insomnia is usually chronic [3–7], with most insomnia patients (85%) reporting that their symptoms have lasted ≥1 year. In fact, in one study, 68% of subjects reported their symptoms lasting ≥5 years, while only 5% had symptoms that lasted 6–12 months, 6% had symptoms lasting for 1–6 months, and just 4% had symptoms for ≤1 month [16].

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What causes insomnia?

Insomnia has many different causes and, according to the origin of the condition, can be divided into three main categories (Fig. 1):

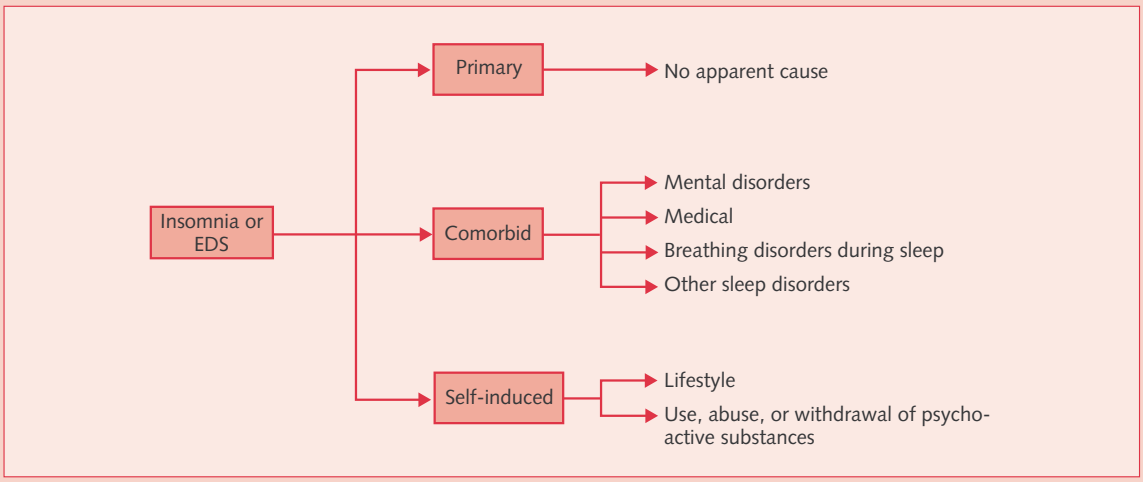
- Comorbid with another physical and/or mental illness.
- Induced by use of psychoactive substances.
- Caused by lifestyle or without apparent cause.

Sleep-related breathing disorders, such as obstructive sleep apnea syndrome (OSAS) or hypoventilation, are thought to account for 5–9% of insomnia complaints (Fig. 2) [8–10]. Periodic limb movement disorders (PLMD), RLS, or both conditions are diagnosed in approximately 15% of individuals who present with insomnia complaints [9–12], while medical or neurological conditions are observed in 4–11% [4,5,9,10]. Poor sleep hygiene or environmental factors are responsible for approximately 10% of insomnia complaints and these symptoms are substance induced in 3–7% [5,9,10,13].

Mental disorders

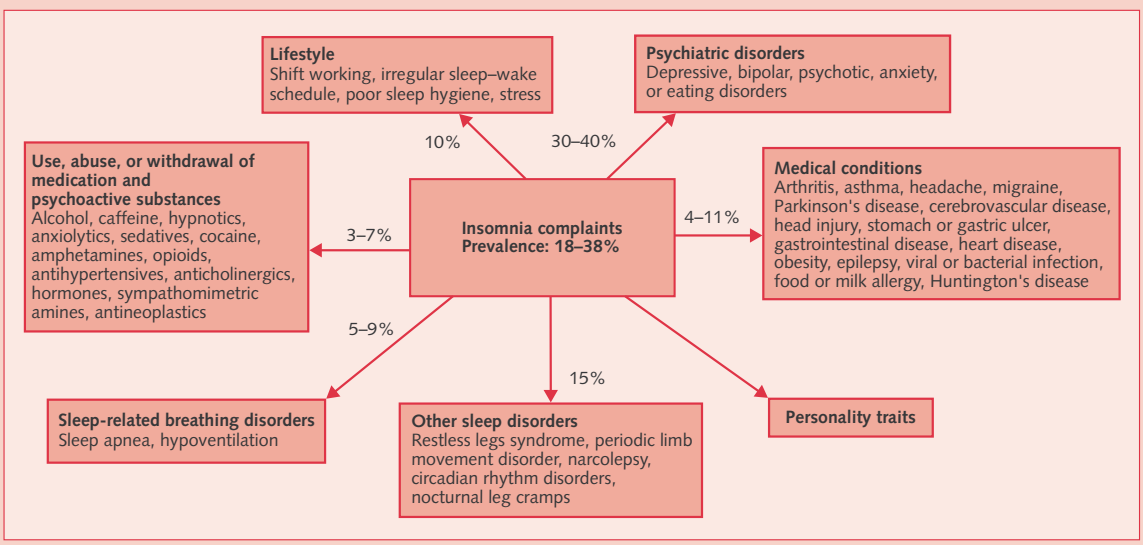
Epidemiological studies have consistently reported that mental disorders are associated with 30–40% of insomnia complaints, and symptoms of mental disorders have been reported to be present in ≥60% of individuals with insomnia symptoms [4,14–17].

Figure 1. Causes of insomnia and EDS.



EDS: excessive daytime sleepiness.

Figure 2. Common causes of insomnia complaints [2].



Medical conditions

In the general population, people with symptoms of insomnia have consistently been found to perceive their health as poorer than the rest of the population [5,17–22] and ≥50% do suffer recurrent, persistent, or multiple health problems [14,23]. The most frequently reported associations are with upper airway diseases [5,24,25], rheumatic diseases [5,24,26,27], chronic pain [26,28], and cardiovascular diseases [5,29,30].

Consequences of insomnia

Development of medical conditions

Several studies have attempted to determine whether insomnia can be responsible for cardiovascular events; however, the results have been inconclusive. One retrospective study found that insomnia was significantly predictive of myocardial infarction [31], and a prospective study reported that the relative risk (RR) of an individual with insomnia developing a

cardiovascular event was 3.1 [29]. Despite these results, three other prospective studies found no relationship between insomnia and the risk of developing a cardiovascular disease [32–34], while another found that there was a greater likelihood of developing insomnia after a cardiovascular event [30].

Development of a mental disorder

Four longitudinal studies have examined the relationship between the persistence of insomnia symptoms and the appearance of mental disorders [35–38]. They found that subjects with insomnia symptoms were 4–8 times more likely to develop a mental disorder during the year following the initial trial interview. Two studies examining the time sequence of the appearance of insomnia symptoms in relation to that of mood and anxiety disorders reported that insomnia was present in 70% of individuals with mood disorders and that it preceded the appearance of the mood disorders in nearly 50% of cases. Insomnia was found in one-third of patients with anxiety disorders and preceded the anxiety disorder in approximately 20% of cases [16,39].

Repercussions for daytime functioning

Insomnia affects the daytime functioning of 20–60% of individuals who suffer this disorder [4,8,40]. Individuals who sleep poorly ≥3 nights per week, are dissatisfied with their sleep, do not feel rested upon awakening, and have hyperarousal in bed are the most likely to experience repercussions in terms of their daytime functioning [4,8].

Road, occupational, and domestic accidents

In the general population, road accidents are experienced 2–3 times more frequently by drivers who report dissatisfaction with their sleep than by those who report sleep satisfaction [8,18]. Such accidents are also more commonly experienced by those with short sleep times (defined as <5 h per night) [41,42]. In the elderly, insomnia is associated with an increased risk of hip fracture [43], and falls [44,45]. Furthermore, the RR for fatal occupational accidents in individuals who have difficulty in sleeping is 1.9 [46].

EDS

Contrary to insomnia, EDS (defined as a propensity for sleep during waking hours) is not a diagnosis. EDS can be a symptom or a consequence of a sleep disorder, physical illness, or mental disorder. However, EDS is a disabling symptom that adversely affects various areas of quality of life and is a good indicator of the presence of health problems. EDS is nearly as prevalent as insomnia, affecting approximately 20% of the general population [47].

What may cause EDS?

Like insomnia, EDS can be comorbid with several disorders – such as organic diseases, mental disorders, or sleep disorders – or can be related to the abuse of, or dependency on, psychoactive substances. EDS can also be induced by the lifestyle of individuals or can be without apparent cause (Fig. 1).

In the general population, physical illnesses account for approximately 20% of EDS complaints, mental disorders for approximately 22%, and sleep disorders – such as OSAS, RLS, and insomnia – for nearly 50%. EDS is an essential criterion for the diagnosis of just three sleep disorders – behaviorally induced insufficient sleep syndrome, hypersomnia (idiopathic, recurrent, or post-traumatic), and narcolepsy. These conditions are diagnosed in <3% of the general population (Fig. 3) [48].

Mental disorders

In epidemiological, cross-sectional studies, 12.4–30% of subjects with EDS have been shown to have a depressive disorder and 20–35% suffer an anxiety disorder [49–52]. However, unlike insomnia, EDS has not been associated with development of a mental disorder in longitudinal studies [35,36,53].

Medical conditions

Several comorbid general medical and neurological disorders can cause EDS (Fig. 3). Studies have shown that the risk of experiencing EDS is 2–4 times greater for individuals with diabetes than for non-diabetics in the general population [52]. Other studies have observed that 16–74% of individuals with Parkinson's disease report EDS [54–56], and that elderly people who complain of EDS are three times more likely to have Alzheimer's disease [57].

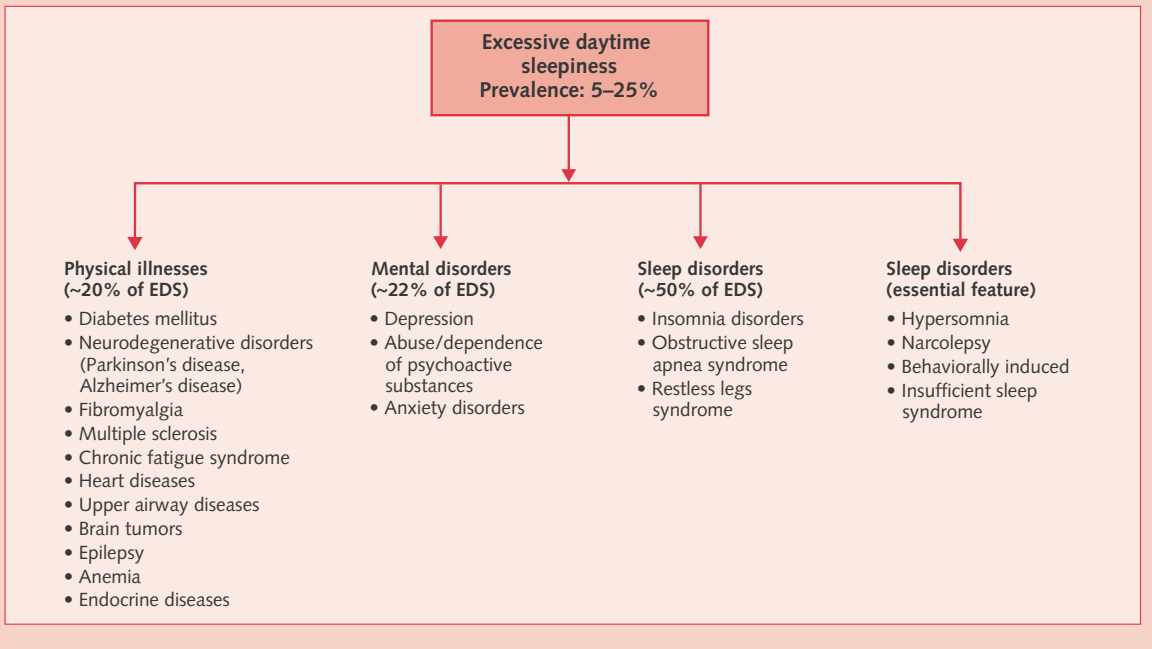
In sleep clinics, OSAS is the most commonly seen cause of EDS, with ≥75% of patients reporting EDS being diagnosed with OSAS. It has been found that up to 25% of individuals in the general population who report EDS have OSAS [49–51,58].

EDS and lifestyle

Unlike insomnia symptoms, EDS is generally not gender-related [50]. Whether its prevalence increases or decreases with age is not clear, as both trends have been observed [48].

Some work schedules, especially shift work, have frequently been linked with EDS. Although some individuals may tolerate the physical strains of shift work, they are not immune to the fatigue, mood swings, reduced performance, and decreased mental agility caused by it. These problems are mainly due to the desynchronization of the circadian rhythm; that is, when the normal sleep/wake rhythm, the normal

Figure 4. Most common causes of excessive daytime sleepiness.



circadian rapid eye movement (REM) sleep rhythm, and the rhythm of REM and non-REM sleep patterns are disrupted. As a consequence, several shift workers complain of excessive sleepiness during working hours and of insomnia during sleeping time. Two studies have reported that up to 30% of night or shift workers report excessive sleepiness at work [18,46].

Epidemiological studies have reported a higher risk of EDS in individuals who use antidepressants, anxiolytics, hypnotics, antihistamines, or alcohol (odds ratio 2–6.7) [4,49,51].

EDS and cognitive deficits

Two epidemiological studies have linked EDS to cognitive deficits. In a study involving 2346 Japanese American men aged 71–93 years, Foley et al. found that those who reported EDS at baseline were twice as likely to be diagnosed with dementia 3 years later than men who did not suffer from daytime sleepiness [59]. Ohayon and Vechierrini performed another study involving 1026 subjects aged ≥60 years and controlled for age, gender, level of physical activity, occupation, organic diseases, use of sleep or anxiety medication, sleep duration, and psychological well-being [60]. They found that subjects with EDS were twice as likely to have attention–concentration deficits, difficulties in orientation, and memory problems as those without EDS.

EDS and mortality

Some population-based studies have investigated the mortality risks associated with EDS. Hays et al. assessed mortality risk in a sample of 3962 elderly individuals (≥65 years) and defined EDS by the presence of naps during the daytime [61]. They found that individuals who reported napping most of the time had a mortality risk of 1.73.

In another study by Rockwood et al., a small increased mortality risk (1.89) from daytime sleepiness was found in their elderly sample [62]. However, this risk did not retain significance when the model was adjusted for age, depression, cognitive deficits, and illness.

Road accidents

EDS has been found to be a direct or contributing factor in 17–21% of road accidents [63,64]. Similarly, road accidents have been found to be experienced 2–3 times more frequently by drivers who have EDS [64,65].

Conclusions

Sleep disturbances are frequently associated with various medical or neurological conditions and psychiatric disorders. Therefore, it is crucial to explore the possibility of comorbid conditions in patients who complain of sleep disturbances. This should be the first step in the planning of an appropriate treatment strategy. Treatment of the comorbid

condition may decrease sleep disturbances; however, in several instances, specific treatment of the sleep disturbances will be necessary and can contribute to the management of the comorbid condition.

Disclosures

Dr Ohayon has no relevant financial relationships to disclose.

References

1. American Sleep Disorders Association Diagnostic Classification Steering Committee. *International Classification of Sleep Disorders: Diagnostic and Coding Manual*. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;**6**:97–111.
3. Ohayon M. Epidemiological study on insomnia in the general population. *Sleep* 1996;**19**:S7–S15.
4. Ohayon MM, Caulet M, Priest RG et al. *DSM-IV* and *ICSD-90* Insomnia symptoms and sleep dissatisfaction. *Br J Psychiatry* 1997;**171**:382–8.
5. Ohayon MM, Zulley J. Correlates of global sleep dissatisfaction in the German population. *Sleep* 2001;**24**:780–7.
6. Ohayon MM, Partinen M. Insomnia and global sleep dissatisfaction in Finland. *J Sleep Res* 2002;**11**:339–46.
7. Ohayon MM. Severe hot flashes are associated with chronic insomnia. *Arch Intern Med* 2006;**166**:1262–8.
8. Ohayon MM, Roth T. What are the Contributing factors for insomnia in the general population? *J Psychosom Res* 2001;**51**:745–755.
9. Buysse DJ, Reynolds CF 3rd, Hauri PJ et al. Diagnostic concordance for *DSM-IV* disorders: a report from the APA/NIMH *DSM-IV* field trial. *Am J Psychiatry* 1994;**151**:1351–60.
10. Jacobs EA, Reynolds CF 3rd, Kupfer DJ et al. The role of polysomnography in the differential diagnosis of chronic insomnia. *Am J Psychiatry* 1988;**145**:346–9.
11. Edinger JD, Fins AI, Goeke JM et al. The empirical identification of insomnia subtypes: a cluster analytic approach. *Sleep* 1996;**19**:398–411.
12. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res* 2002;**53**:547–54.
13. Ohayon MM. Prevalence of *DSM-IV* diagnostic criteria of insomnia: distinguishing between insomnia related to mental disorders from sleep disorders. *J Psychiatr Res* 1997;**31**:333–46.
14. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment: prevalence and correlates. *Arch Gen Psychiatry* 1985;**42**:225–32.
15. Ohayon MM, Caulet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry* 1998;**39**:185–97.
16. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res* 2003;**37**:9–15.
17. Maggi S, Langlois JA, Minicuci N et al. Sleep complaints in community-dwelling older persons: prevalence, associated factors, and reported causes. *J Am Geriatr Soc* 1998;**46**:161–8.
18. Ohayon MM, Lemoine P, Arnaud-Briant V et al. Prevalence and consequences of sleep disorders in a shift worker population. *J Psychosom Res* 2002;**53**:577–83.
19. Barbar SI, Enright PL, Boyle P et al. Sleep disturbances and their correlates in elderly Japanese American men residing in Hawaii. *J Gerontol A Biol Sci Med Sci* 2000;**55**:M406–11.
20. Kim K, Uchiyama M, Okawa M et al. An epidemiological study of insomnia among the Japanese general population. *Sleep* 2000;**23**:41–7.
21. Chiu HF, Leung T, Lam LC et al. Sleep problems in Chinese elderly in Hong Kong. *Sleep* 1999;**22**:717–26.
22. Blazer DG, Hays JC, Foley DJ. Sleep complaints in older adults: a racial comparison. *J Gerontol A Biol Sci Med Sci* 1995;**50**:M280–4.
23. Bixler EO, Kales A, Soldatos CR et al. Prevalence of sleep disorders in the Los Angeles metropolitan area. *Am J Psychiatry* 1979;**136**:1257–62.
24. Gislason T, Almqvist M. Somatic diseases and sleep complaints: an epidemiological study of 3201 Swedish men. *Acta Med Scand* 1987;**221**:475–81.
25. Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. *Chest* 1987;**91**:540–6.
26. Sutton DA, Moldofsky H, Badley EM. Insomnia and health problems in Canadians. *Sleep* 2001;**24**:665–70.
27. Hagen KB, Kvien TK, Bjørndal A. Musculoskeletal pain and quality of life in patients with noninflammatory joint pain compared to rheumatoid arthritis: a population survey. *J Rheumatol* 1997;**24**:1703–9.
28. Andersson HI, Ejlertsson G, Leden I et al. Impact of chronic pain on health care seeking, self care, and medication. Results from a population-based Swedish study. *J Epidemiol Community Health* 1999;**53**:503–9.
29. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. *J Intern Med* 2002;**251**:207–16.
30. Foley DJ, Monjan A, Simonsick EM et al. Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6800 persons over three years. *Sleep* 1999;**22**(Suppl 2):366–72.
31. Falger PR, Schouten EG, Appels AW et al. Sleep complaints, behavioral characteristics and vital exhaustion in myocardial infarction cases. *Psychology & Health* 1988;**2**:231–58.
32. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *Am J Epidemiol* 1992;**135**:854–64.
33. Koskenvuo M, Kaprio J, Lönnqvist J et al. Social factors and the gender difference in mortality. *Soc Sci Med* 1986;**23**:605–9.
34. Schwartz SW, Cornoni-Huntley J, Cole SR et al. Are sleep complaints an independent risk factor for myocardial infarction? *Ann Epidemiol* 1998;**8**:384–92.
35. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989;**262**:1479–84.
36. Breslau N, Roth T, Rosenthal L et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;**39**:411–8.
37. Roberts RE, Roberts CR, Chen IG. Impact of insomnia on future functioning of adolescents. *J Psychosom Res* 2002;**53**:561–9.
38. Roberts RE, Shema SJ, Kaplan GA. Sleep complaints and depression in an aging cohort: a prospective perspective. *Am J Psychiatry* 2000;**157**:81–8.
39. Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. *J Psychiatr Res* 2006;**40**:700–8.
40. Leger D, Guilleminault C, Dreyfus JP et al. Prevalence of insomnia in a survey of 12,778 adults in France. *J Sleep Res* 2000;**9**:35–42.
41. Connor J, Norton R, Ameratunga S et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. *BMJ* 2002;**324**:1125.
42. McCartt AT, Ribner SA, Pack AI et al. The scope and nature of the drowsy driving problem in New York State. *Accid Anal Prev* 1996;**28**:511–7.
43. Fitzpatrick P, Kirke PN, Daly L et al. Predictors of first hip fracture and mortality post fracture in older women. *Ir J Med Sci* 2001;**170**:49–53.
44. Brassington GS, King AC, Bliwise DL. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. *J Am Geriatr Soc* 2000;**48**:1234–40.
45. Méndez Rubio JI, Zunzunegui MV, Béland F. The prevalence of and factors associated with falls in older persons living in the community. *Med Clin (Barc)* 1997;**108**:128–32.
46. Akerstedt T, Knutsson A, Westerholm P et al. Sleep disturbances, work stress and work hours: a cross-sectional study. *J Psychosom Res* 2002;**53**:741–8.
47. Ohayon MM. Epidemiology of excessive daytime sleepiness. *Sleep Med Clin* 2006;**1**:9–16.
48. Ohayon MM. From wakefulness to excessive sleepiness: what we know and still need to know. Sleep Med Rev. 2008;**12**:129-41.
49. Hublin C, Kaprio J, Partinen M. Daytime sleepiness in an adult, Finnish population. *J Intern Med* 1996;**239**:417–23.
50. Ohayon MM, Caulet M, Philip P et al. How sleep and mental disorders are related to complaints of daytime sleepiness. *Arch Intern Med* 1997;**157**:2645–52.
51. Nugent AM, Gleadhill I, McCrum E et al. Sleep complaints and risk factors for EDS in adult males in Northern Ireland. *J Sleep Res* 2001;**10**:69–74.
52. Bixler EO, Vgontzas AN, Lin HM et al. EDS in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005;**90**:4510–5.
53. Hasler G, Buysse DJ, Gamma AJ. EDS in young adults: a 20-year prospective community study. *J Clin Psychiatry*. 2005;**66**:521–9.
54. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. *Mov Disord* 1999;**14**:9227.
55. Hobson DE, Lang AE, Martin WR. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* 2002;**287**:455–63.
56. Kumar S, Bhatia M, Behari M. Excessive daytime sleepiness in Parkinson's disease as assessed by Epworth Sleepiness Scale (ESS). *Sleep Med* 2003;**4**:339–42.
57. Bonanni E, Maestri M, Tognoni G et al. Daytime sleepiness in mild and moderate Alzheimer's disease and its relationship with cognitive impairment. *J Sleep Res* 2005;**14**:311–7.
58. Janson C, Gislason T, De Backer W et al. Daytime sleepiness, snoring and gastro-oesophageal reflux amongst young adults in three European countries. *J Intern Med* 1995;**237**:277–285.
59. Foley D, Monjan A, Masaki K . Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J Am Geriatr Soc* 2001;**49**:1628–32
60. Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. *Arch Intern Med* 2002;**162**:201–8.
61. Hays JC, Blazer DG, Foley DJ. Risk of napping: EDS and mortality in an older community population. *J Am Geriatr Soc* 1996;**44**:693–8.
62. Rockwood K, Davis HS, Merry HR et al. Sleep disturbances and mortality: results from the Canadian Study of Health and Aging. *J Am Geriatr Soc* 2001;**49**:639–41.
63. Lyznicki JM, Doege TC, Davis RM et al. Sleepiness, driving, and motor vehicle crashes. Council on Scientific Affairs, American Medical Association. *JAMA* 1998;**279**:1908–13.
64. Garbarino S, Nobili L, Beelke M et al. The contributing role of sleepiness in highway vehicle accidents. *Sleep* 2001;**24**:203–6
65. Howard ME, Desai AV, Grunstein RR. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *Am J Respir Crit Care Med* 2004;**170**:1014–21.

Family, Health, and Identity: A Case of Inherited Obstructive Sleep Apnea

CASE STUDY

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In the midst of a busy day seeing patients, being both a good listener and an efficient healthcare provider can be a challenge. The multiple roles physicians juggle with credentialing rules, quality-assurance measures, and productivity demands can be daunting. On such stressful days, it is increasingly difficult for physicians to remember the human experience of healing that drew us to this profession. This, coupled with the long hours, exhaustion, and, at times, thanklessness can result in both poor patient care and physician burnout. However, recently I met a remarkable patient who reminded me of the importance of what we do by carefully highlighting how a disease has shaped his life. He reminded me that even when we physicians feel that our job as listener of complaints and symptoms becomes mundane, we are obliged to examine a little more closely and to recognize the intimate piece of history that we are invited to become a part of, as well as the corresponding significance of the role we play in our patients' lives. Illness can play a crucial role in the formation of identity. If we listen to who a person is, we may discover the key to their diagnosis. *Int J Sleep Wakefulness – Prim Care* 2008;**1**(4):146–8.

David Vick was the third of three children born into a working-class family of Norwegian descent in Madison, WI, USA, in 1931. When David was 3 years of age, his father, a rate investigator for the Wisconsin Railroad Commission, died of pneumonia aged 48 years. David's paternal grandfather also died at a very young age, coincidently when his father was also 3 years old, and David describes growing up without a father as one of the events that shaped his life.

David was a sickly child with delayed growth. At 12 years of age he was bed bound for 5 weeks when he developed pneumonia. He vividly remembers his doctor making house calls, and his deconditioning. This may have been the beginning of his lifelong fear of catching a life-threatening respiratory illness, like those that took the lives of his father, paternal grandfather, and grandmother. After David recovered, he became an honor-roll high-school student and later graduated from the University of Wisconsin, with a degree in accounting. He was able to obtain a student deferment to avoid the Korean War draft until 1953 and was anxious about military service because of his family history of respiratory illness. Six of his schoolmates who became infantrymen died in Korea and, from talking with returned combat veterans, he became aware that the cold weather exposure of an infantryman would be difficult for him to tolerate due to his susceptibility to respiratory illnesses. He therefore joined the Navy and became a supply officer aboard a destroyer warship. Although armistice had occurred by that time, the Navy kept him at sea for 3 years. During these years his respiratory status was worsened by continuous exposure to black oil and gunpowder fumes.

After the war David took a job with IBM in San Francisco, CA, but in 1959 arranged a transfer back to Madison to live with his ailing mother. When his mother was 72 years old, and David 30 years, she died of kidney disease. David's maternal ancestors had round faces and long lives, while his paternal grandparents had long faces and short lives, as can be seen in Figure 1.

David married at the age of 32, but the marriage did not last long. When it ended David moved back to California, became a social worker and began working at a family service agency. The decision to move to California was mainly a result of his intolerance to cold weather and the accompanying illnesses. He was finding that his fear of falling ill with a life-threatening respiratory disease was becoming severely restrictive.

By chance, in 1991 David heard a lecture given by Dr William Dement at Stanford University (Stanford, CA, USA) about obstructive sleep apnea (OSA) and its associations with obesity, excessive daytime sleepiness, and snoring. David was an exceptionally fit, passionate runner, and thought he had none of the symptoms Dr Dement had

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Figure 1. Pictorial family tree. A similarity can be seen between the jaw shape of David Vick, his father, and also perhaps his grandfather.

GREAT GRANDFATHER
Paul Olson Syftestad
1816–1902 86 years
Arteriosclerosis

GREAT GRANDFATHER
Ole Arneson Røste
1827–1903 75 years
Pneumonia

GREAT GRANDMOTHER
Anna Slimsa Røste
1828–1920 92 years
Bronchitis

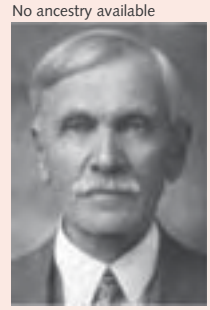
GREAT GRANDFATHER
Bjørgo Larson
1835–1929 93 years
Fracture colli femoris

GREAT GRANDMOTHER
Ingeborg Wilson Larson
1840–1921 80 years
Aortic regurgitation

GRANDFATHER (Paternal)
REV. Olaus P. Syftestad
1857–1890 32 years
Pneumonia

GRANDMOTHER (Paternal)
Sarah Røste Syftestad
1864–1922 58 years
Pneumonia

No ancestry available



GRANDFATHER (Maternal)
Andrew Trovaten Vick
1854–1942 88 years
Cerebral thrombosis

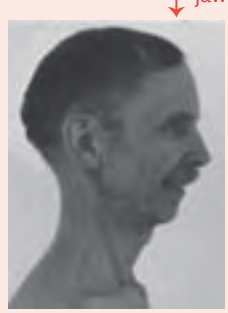
GRANDMOTHER (Maternal)
Julia Larson Vick
1862–1947 85 years
Myocardial insufficiency

FATHER Ole Selmer Syftestad
1886–1934 48 years
Pneumonia

Note similar jaws

MOTHER Lydia Vick Syftestad
1888–1961 72 years
Kidney disease (Chronic pyelonephritis)

PATIENT David Vick Syftestad
a.k.a. David Syftestad Vick
b. 1-14-1931 66 years



David 61 years

David 39 years

David 27 years

described. However, he did consider himself an early morning "light" sleeper his entire life and did take naps some afternoons. In 1995 he volunteered to take part in an insomnia research study but was rejected when a take-home sleep study revealed OSA. At the time, he did not realize the significance of this result or the fact that OSA could be tied to his other medical conditions. His internist referred him to a pulmonologist, who performed a bronchoscopy. He was found to have chronic obstructive pulmonary disease (COPD) and gastresophageal reflux. He then saw a gastroenterologist who diagnosed him with a dilated esophagus and poor peristalsis and he was referred to the Stanford Sleep Disorders Clinic. Although he was extremely fit and slim, his sleep study results showed that he did have mild OSA with an apnea–hypopnea index (AHI) of 11.7 events/h. He was treated with rudimentary (by today's standards) continuous positive airway pressure.

Although he had never considered sleepiness a problem in his life, within 3 months he noticed a huge improvement in daytime functioning. Like many patients with OSA, David had not been aware of the degree of impairment until it was remedied. After 1 year of treatment, others commented on his increased energy and the fact that, for once in his life, he "looked good." He no longer suffered from early morning insomnia. Upon researching his condition, he found that OSA was known to occur in families – primarily as a result of the inheritance of craniofacial structures, and especially that of a small lower jaw. He looked through family photographs and found that his jaw structure looked similar to that of his father and paternal grandfather. Both his father and paternal grandfather died prematurely of pneumonia, which prompted David to wonder whether they had suffered from gastresophageal reflux resulting in COPD and a susceptibility to pneumonia like himself.

Untreated OSA can cause gastresophageal reflux and, although OSA had not yet been described in 1890 or 1934 when they died, it is very likely that David's father and grandfather had this condition. Figure 1 shows the similar jaws of David, his father, Ole, and perhaps also his grandfather, Olaus. David now had good reason to believe that his father's and his grandfather's deaths from pneumonia were not just random events, but likely due to inherent craniofacial structures resulting in OSA. He felt that through his diagnosis at the Stanford clinic, he had come to understand himself and his family better, and is very grateful for this insight.

Following 1 year of treatment for OSA, a repeat bronchoscopy showed that David's airways had radically improved. He felt significantly better and was amazed that a sleep disorder could be the cause of his illness; as a result he became increasingly involved in the Stanford Sleep Disorders Clinic. He now leads an OSA awareness group for patients and has donated both time and money to the clinic with the aim of increasing the awareness of sleep disorders, with a particular focus on the identification of these illnesses in patients with atypical presentations or non-traditional features.

David feels that his life has been impacted by quick judgments and prejudice. Previously, no one had considered a diagnosis of OSA because he was young and thin. Nor had they thought of it before he suffered repeated bouts of pneumonia and had to accept the untimely death of his father and his grandfather. No one had thought of it before he had learnt that connecting with others meant exposures and had developed the habit of obsessing over risk and threats, connecting them to his familial susceptibility to respiratory illnesses. David feels strongly that having OSA, especially as a familial trait, has radically shaped who he is as a person, not necessarily because of the treatment he has had or the symptoms, but because he believes OSA played a role in his father's untimely death and that it impacts his relationships with other people.

When I first met David, I couldn't help noticing his soft-spoken voice and concern for everything around him. He describes himself as liberal, persistent, and kind. He has no doubt that his predisposition for respiratory illnesses and fears are directly linked to his OSA – as are the untimely deaths of his father and grandfather. To me, his lifelong concern about contracting respiratory-related illnesses is manifest in his vigilant tendency to wash his hands, keep a certain distance from others, avoid travel, and meticulously examine everything around him. He states simply that contracting pneumonia, which he has had five times, has been a major concern for most of his life. So much so that he had agonized over a way in which to politely avoid shaking hands.

Conclusion

David Vick, like many people, has been shaped by the consequence of illness. His health has shaped who he is, and it is of paramount importance to him that everyone learns about sleep apnea. I believe that there is something to learn from people who have been so dramatically shaped by a disease. We, as physicians, are called upon to learn from the experiences of our patients, pass on their messages, and give them a voice. In David Vick's case, it is the message that young, thin, and fit individuals can have OSA, and that it can be a debilitating, life-shaping illness if not identified and treated.

Disclosures

The authors have no relevant financial relationships to disclose.

CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

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

SLEEP-DISORDERED BREATHING

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

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

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

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

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

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

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

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Effect of a 2 week CPAP treatment on mood states in patients with obstructive sleep apnea: a double-blind trial.

Haensel A, Norman D, Natarajan L et al.
Sleep Breath 2007;**11**:239–44.

In a placebo-controlled study, 50 individuals with untreated obstructive sleep apnea were randomized to receive either therapeutic or placebo continuous positive airway pressure (CPAP) for 2 weeks. Both the therapeutic and placebo CPAP groups showed significant improvements in the Profile of Mood States total score, with no differences observed between the two groups.

There is a high prevalence of mood disorders in patients with obstructive sleep apnea (OSA), and previous studies assessing the effect of continuous positive airway pressure (CPAP) on mood have been inconclusive. The authors of this study therefore performed a placebo-controlled trial to assess the effect of 2 weeks of CPAP treatment on various aspects of mood. Previously, the same authors conducted a similar placebo-controlled study examining the effect of 1 week of

CPAP treatment on mood but observed no significant changes [1].

The present study included 50 participants ranging from 30–65 years of age with OSA (defined as an apnea–hypopnea index [AHI] of ≥15 events/h). Subjects were randomized into two treatment groups; one received therapeutic CPAP while the other was given sham treatment. All patients completed the Profile of Mood States (POMS) questionnaire to assess psychological distress both pre- and post-treatment. Patients with a history of depression were excluded from the study. Both groups underwent formal CPAP titration nights, with the placebo group being delivered <1 cmH_2O pressure. CPAP compliance data was obtained after the 2-week trial period and showed no significant differences between the two groups with regard to nighttime CPAP use. Both the patients using therapeutic and placebo CPAP showed significant improvements on four of the seven POMS mood ratings – tension, fatigue, confusion, and total scores without a time × treatment interaction.

The small sample size and limited observation period are drawbacks of this study. Although the effects of CPAP on energy level may be immediately evident, neurocognitive and behavioral effects may take time to develop. CPAP can alter a variety of metabolic and physiological parameters over time. For instance, CPAP can induce weight loss that may alter self image and, hence, affect mood as well.

1. Yu BH, Ancoli-Israel S, Dimsdale JE. Effect of CPAP treatment on mood states in patients with sleep apnea. *J Psychiatr Res* 1999;**33**:427–32.

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Long-term effect of continuous positive airway pressure on BP in patients with hypertension and sleep apnea

Campos-Rodriguez F, Perez-Ronchel J, Grilo-Reina A et al.
Chest 2007;**132**:1847–52.

These authors measured blood pressure (BP) before and after 24 months of continuous positive airway pressure therapy in patients with obstructive sleep apnea and hypertension. Changes in diastolic BP were observed and a subgroup demonstrated additional improvements in BP parameters. Circadian rhythmicity of BP was observed in a greater proportion of patients after treatment.

Obstructive sleep apnea (OSA) is a risk factor for hypertension and mixed evidence exists concerning the impact of continuous positive airway pressure (CPAP) therapy for OSA on hypertension. The authors of this non-controlled study investigated whether patients with OSA and hypertension experienced reduced blood pressure (BP) following 24 months of CPAP use.

Participants comprised 70 patients with suspected OSA recruited from the sleep disorders unit of an academic hospital. In all, 55 patients (aged 57.2±7.5 years, 64% male) completed ambulatory BP monitoring (ABPM) before initiation of CPAP and at 24-month follow-up.

Patients reported 5.3±1.9 h/day of CPAP use; 27% reported a change in antihypertensive medication since baseline. Diastolic BP decreased by –2.2 mmHg from baseline (95% confidence interval –4.2 to –0.1; p=0.03). Although there were no other significant reductions in ABPM parameters, better CPAP compliance was correlated with greater reductions in 24-h mean arterial pressure (r=–0.30; p=0.02), as were higher baseline systolic BP (r=–0.43; p=0.001) and diastolic BP (r=–0.38; p=0.004). In a subgroup of 35 patients with incompletely controlled baseline hypertension, significant reductions in all ABPM parameters were observed. Although just 18% of participants demonstrated a normal circadian reduction in nocturnal BP at baseline, 53% showed this "dipping pattern" at follow-up (p=0.0006).

The lack of a control group and change in antihypertensive medications before follow-up preclude attributing the observed changes to CPAP.

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Obstructive sleep apnea and resistant hypertension: a case-control study

Gonçalves SC, Martinez D, Gus M et al.
Chest 2007;**132**:1858–62.

To determine the extent of the association between obstructive sleep apnea syndrome (OSAS) and resistant hypertension, the authors of this study utilized a case-control design to eliminate confounding factors. In total, 63 patients with resistant hypertension despite anti-hypertensive therapy, and 63 with medically controlled hypertension, underwent ambulatory polysomnography. Results suggested a strong association between OSAS and resistant hypertension, with the prevalence of the resistant hypertension increasing with the severity of OSAS.

As numerous studies have illustrated, a relationship exists between the presence of resistant hypertension and obstructive sleep apnea syndrome (OSAS). However, as studies of this association have not accounted for confounders or used control groups, the evidence remains limited. The present authors examined a control group of patients with non-resistant

hypertension along with resistant hypertensive patients to eliminate the effect of factors that could affect this relationship.

Sixty-three patients aged 40–70 years with a body mass index (BMI) of 25–40 kg/m^2 and resistant hypertension were recruited. Resistant hypertension was defined as a blood pressure (BP) of ≥140/90 mmHg, despite using at least three anti-hypertensive medications. Those with secondary hypertension were excluded. Resistant patients were matched by age, gender, and BMI with 63 participants who had controlled blood pressure. Exclusion criteria included patients suspected of non-compliance to therapy, who had a previous diagnosis of a sleep disorder, or who had any other disease associated with OSAS. All patients had BP readings taken in the office and underwent an ambulatory polysomnography (PSG) as well as 24-h ambulatory BP monitoring (ABPM). The authors then analyzed and compared the proportion of patients with OSAS who were hypertensive either in the office reading, during the ABPM, during both, or not at all.

Results revealed that OSAS was present in 71% of the resistant hypertension patients and 38% of control subjects, using an apnea–hypopnea index (AHI) >10 events/h as the threshold for diagnosis. The association between OSAS and resistant hypertension was statistically significant, with the frequency of resistant hypertension increasing with the severity of OSAS. The lowest AHI and lowest prevalence of OSAS was found in the group who had normal BP during both ABPM and in the office. Furthermore, the prevalence of OSAS was lower in women in both resistant hypertensive and control groups, even though the magnitude of risk revealed no gender bias.

The findings confirm the robust relationship between OSAS and hypertension in a case-control study design. Future studies assessing the efficacy of continuous positive airway pressure (CPAP) in such a setting would be useful.

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

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

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

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

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

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

The 10 studies included a total of 562 children with OSA, 93 children with juvenile rheumatoid arthritis (JRA), and 815 healthy children. In eight of the 12 CHQ subscale QoL items, scores of children with OSA were significantly lower than those of healthy children, particularly with respect to the CHQ QoL subscales of general health perceptions and parental impact-emotional ($p<0.001$ for both). Two studies compared CHQ QoL scores for OSA and JRA, and found that – with the exception of subscales of parental impact-emotional and parental impact-time, which both significantly yielded lower scores for children with OSA ($p<0.05$ for both) – children with OSA had a similarly low QoL as those with JRA. Short- and long-term outcomes following adenotonsillectomy were reported in seven and two studies, respectively. Overall, significant improvements in both short- and long-term QoL were observed following surgery, with the most significant changes made in sleep disturbance, caregiver concerns, and physical suffering. Furthermore, there were no significant differences between short-term and long-term scores.

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

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SLEEP-RELATED MOVEMENT DISORDERS

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

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

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

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

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

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

It is interesting to see an increase in the rate of diagnosis of this condition, which may reflect a rise in awareness. However, the increased use of medications and referrals before diagnosis indicates that patients were investigated for several conditions before a diagnosis of RLS was made. The authors conclude that medications not approved for the treatment of RLS are not associated with a reduction in clinical symptoms or use of healthcare resources.

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

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

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

An association between cardiovascular disease (CVD) and restless leg syndrome (RLS) has been indicated in two epidemiological studies [1,2]. However, the diagnostic criteria for RLS have changed since these analyses were published, and one of the studies included data only from men. The mechanism underlying a relationship between CVD and RLS is unclear, but may involve repetitive electroencephalograhic arousals, substantial autonomic hyperactivity, or sleep deprivation.

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

The investigators determined that RLS was present in 5.2% of this cohort, and affected 6.8% of women and 3.3% of men. The demographic characteristics of subjects with and without RLS were similar, although those without RLS were more likely to consume >1 alcoholic drink per day. CVD was experienced by 29.6% and 19.5% of RLS and

non-RLS subjects, respectively. The following variables were also associated with a significantly higher risk of CVD:

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

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

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

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

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

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

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

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

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

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

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

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

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INSOMNIA

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

Krystal AD, Erman M, Zammit GK et al; ZOLONG Study Group.

Sleep 2008;**31**:79–90.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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EXCESSIVE DAYTIME SLEEPINESS

Placebo and modafinil effect on sleepiness in obstructive sleep apnea

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

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

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

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

Twenty-two patients with OSA who were currently receiving CPAP treatment were enrolled in the study. All patients had an Epworth Sleepiness Score (ESS) >10.

Subjects received blinded placebo treatment for 7 days and were then randomized to receive either placebo (n=11) or modafinil (300 mg/day; n=9) for a further 21 days. Patients were evaluated at baseline, randomization, and study end using the ESS, maintenance of wakefulness test, and Short-Form 36, among others.

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

The authors conclude that modafinil, used adjunctively with CPAP therapy, improves EDS in patients suffering from OSA. They highlight the importance of including a blinded placebo period prior to randomization to fully observe the placebo effect, and suggest that a similar process should be performed in other drug trials that are based on measures of subjective response.

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Patient-management strategies

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

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

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

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

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

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

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

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PEDIATRIC SLEEP

DSM-IV diagnoses and obstructive sleep apnea in children before and 1 year after adenotonsillectomy

Dillon JE, Blunden S, Ruzicka DL et al.
J Am Acad Child Adolesc Psychiatry 2007;**46**:1425–36.

The current study examined *Diagnostic and Statistical Manual of Mental Disorders-IV*-based diagnosis of psychiatric disorders among children who had been referred for adenotonsillectomy. The results indicated a reduction in disruptive behavior 1 year post-surgery. Obstructive sleep apnea based on polysomnography was also analyzed.

Previous studies have revealed that sleep-deprived children mask sleepiness with hyperactivity along with problems with

mood and anxiety that often improve with treatment of the sleep difficulty. Children with reported obstructive sleep apnea (OSA), either through a clinical diagnosis or polysomnography (PSG)-based criteria, often benefit from adenotonsillectomy. The current investigators explored the relationship between psychiatric morbidity and OSA at baseline and at a 1-year follow-up post-adenotonsillectomy.

Children in the study group (n=79; n=78 at follow-up) had been referred for adenotonsillectomy; those in the control group (n=27; n=23 at follow-up) had been referred for unrelated surgical conditions. Both groups excluded children with pre-existing psychiatric conditions, severe medical conditions, and history of treatment for sleep-disordered breathing. The computerized Diagnostic Interview Schedule for Children (DISC) was used to obtain diagnoses of attention and disruptive behavior disorders. Several other instruments were also utilized to gain an accurate diagnosis for each child.

Unsurprisingly, 36.7% of children referred for adenotonsillectomy were attributed at least one attention or disruptive behavior diagnosis at baseline, compared with 11.1% of the control group. A significant drop in disruptive behavior was found at follow-up in the study group, while the control group had little variation, resulting in no significant difference between the groups at follow-up. Within the study group OSA severity had no significant relationship to behavioral ratings except for a slight correlation with oppositional behavior.

Interestingly, OSA did not predict the psychopathology of children in the study group either at baseline or at follow-up. The current study aids the sparse literature in the understanding of the psychopathology of children who demonstrate symptoms of sleep disorders. When presented with certain behavioral problems in children, it is important to be attentive to potential OSA symptoms and physical signs.

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Immediate as well as delayed post learning sleep but not wakefulness enhances declarative memory consolidation in children

Backhaus J, Hoeckesfeld R, Born J et al.
Neurobiol Learning Mem 2008;**89**:76–80.

In this study, children underwent a word-pair recall task and were then tested after a period of wakefulness or sleep. Memory was significantly increased only after the sleep period, indicating that, in line with the findings in adults, sleep is involved in declarative memory consolidation in this study.

There has been a great deal of recent research suggesting that sleep plays an important role in memory consolidation. This has included evidence that sleep improves the consolidation of both procedural and declarative memory. However, there have been no studies to examine this phenomenon in children. This investigation by Backhaus and colleagues is the first to examine the role of sleep on memory consolidation in children.

In this study, 27 children between the ages of 9 and 12 years were evaluated in a word-pair recall task. Half of the subjects were trained prior to going to bed at night and then tested the next morning and next evening (sleep–wake condition), while the other half underwent training in the morning with their first test session in the evening and second after a night's sleep (wake–sleep condition).

The authors found that recall was significantly higher after sleep than after wakefulness, independent of whether the subjects were in the sleep–wake or wake–sleep condition. However, it should be noted that the improvement with sleep in the wake–sleep condition was relatively small compared with that in the sleep–wake group.

The authors conclude that, consistent with the evidence in adults, these findings indicate that sleep played an active role in declarative memory consolidation in this study.

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MISCELLANEOUS

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

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

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

Studies on sleep–wake misperception, or paradoxical insomnia as it is now referred to according to the second edition of the International Classification of Sleep Disorders, have investigated several aspects of the perception of sleep. Many of these past studies have focused on a subject's ability to identify an arousal, either deliberate or spontaneous, by pressing a button. These studies have confirmed that accuracy relies on the stage of

sleep a subject is in at the time of the arousal, with rapid eye movement (REM) sleep being the most accurate. The current authors collected data on deliberate awakenings from randomized subjects in stage two and REM sleep.

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

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

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

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

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

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

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

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

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

Bad dreams were reported to be relatively rare occurrences in children aged 29 months to 6 years, with between 1.7% and 3.9% of respondents reporting that bad dreams occurred always or often. The presence of bad dreams appears to be a relatively stable characteristic, and becomes more so over time. This may indicate that these dreams will continue into adolescence and adulthood and, therefore, that children may benefit from early intervention. Despite studies of older children indicating a higher prevalence of bad dreams amongst girls, particularly in adolescence, no gender-related differences were found in the prevalence of bad dreams among preschool-aged children. High family income, absence of siblings and a non-immigrant mother were all associated with bad dreams at 29 months. At the 29- and 41-month assessments, parental nurturing after awakening, sleep onset nurturance, a difficult temperament at 5 months, and anxiousness at 17 months was associated with bad dreams.

Bad dreams occur less frequently in children aged <6 years than the authors expected. As the occurrence of bad dreams seemed to be a trait-like characteristic, it is possible that early intervention could prevent these from re-occurring at a later stage in their lives. However, as this trial was the first study examining these parameters in such young children, the results will need to be confirmed in further investigations.

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Short sleep times predict obesity in internal medicine clinic patients

Buscemi D, Kumar A, Nugent R et al.
J Clin Sleep Med 2007;**3**:681–8.

The objective of this study was to determine whether an association exists between short sleep times and obesity, as defined by body mass index in patients with concomitant medical conditions. Completed questionnaires from 200 participants with various chronic medical diagnoses were analyzed, and the findings adjusted for age and certain related medical conditions. Results revealed that subjects with short sleep times (<7 h) had an increased propensity for obesity, with a U-shaped relationship between hours of sleep in women, but not in men.

Although numerous studies have clearly established a relationship between shorter sleep times and obesity (as defined by body mass index [BMI]), relatively few have demonstrated this relationship in obese patients with chronic medical conditions. This study attempted to delineate such a relationship by examining continuity-of-care clinical patients and surveying their sleep habits, lifestyle characteristics, and medical diagnoses.

Two hundred individuals with chronic medical conditions were surveyed and classified as either not obese (BMI <30 kg/m^2) or obese (BMI ≥30 kg/m^2). Analysis was adjusted for age, lifestyle characteristics, and various medical diagnoses such as diabetes mellitus, hypertension, coronary artery disease, heart failure, arthritis, sleep apnea, and chronic obstructive pulmonary disease (COPD). The median age of the cohort was 54 years (range 18–89 years), the mean BMI was 30.1±7.9 kg/m^2, and the mean total sleep time was 7.89±1.91 h. In all, 82 patients (41.2%) were classified as obese

Results revealed that short sleep times (<7 h compared with 8–9 h) increased the likelihood of obesity. Sleep apnea and hypertension also increased the likelihood of obesity in women, as did alcohol consumption and diabetes in men, and alcohol consumption and sleep apnea in older patients (≥50 years of age). Interestingly, although short and long sleep times were both associated with obesity in women in a "U-shaped" relationship, no such pattern was evident for men. The authors also attempted to determine factors that could explain the relationship between obesity and shortened hours of sleep, such as increased opportunities for food consumption, the complex interaction between sleep and disease chronicity, and, more persuasively, the interaction between hormones, appetite regulation, and sleep, which has been demonstrated in other studies.

Ultimately, however, this study suffers from numerous limitations, one being the use of self-reported questionnaires as opposed to objective polysomnographies, which could have confirmed bed-time patterns as well as the presence of objectively determined sleep-disordered breathing. In addition, as the quality of sleep itself was not examined, it is difficult to surmise the extent to which this factor contributes to obesity. Furthermore, to delineate the role of hormones in the relationship between sleep and obesity in this population, it would have been beneficial to assess the levels of hormones, such as leptin and ghrelin, which regulate appetite and are influenced by sleep.

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