Sleep-Disordered Breathing in Pregnancy

Bilgay Izci Balserak

Relationship Between Attention-Deficit Hyperactivity Disorder and Sleep Disturbances

Eric Konofal

Impact of Insomnia: Wide-Reaching Burden and a Conceptual Framework for Comorbidity

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Faculty Disclosures

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


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

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


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

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

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

Pedram Navab, DO: Cephalon, Jazz Pharmaceuticals.


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

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

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Design and Artwork: AS&K Skylight Creative Services

1754-307X
Contents

Leading Articles
Sleep-Disordered Breathing in Pregnancy 98
Bilgay Izci Balserak

Relationship Between ADHD and Sleep Disturbances 109
Eric Konofal

Impact of Insomnia: Wide-Reaching Burden and a Conceptual Framework for Comorbidity 118
Wallace Mendelson

Clinical Reviews
Sleep-Disordered Breathing 124
Movement Disorders 127
Epidemiology 128
Insomnia 130
Narcolepsy 131
Clinical Management 133

Meeting Report
worldsleep07: The 5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies Cairns, QLD, Australia, September 2–6, 2007 136

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

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

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

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

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

Reasons for such disturbances in the third trimester include [1–3,5–8,10,12,15,16]:

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

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

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

Manifestations of SDB in pregnancy

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

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

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

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

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

Obstructive sleep apnea and oxygen desaturation during pregnancy and post partum

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

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

In a larger study, PSG was performed with an esophageal manometry test on a subgroup of 26 women after the 6th month of pregnancy; this selection comprised 13 loud snorers and 13 non-snorers [24]. None of these women had frank OSA, but airflow limitation and increased respiratory effort were common. In the same study, 13% of 267 pregnant women had arterial oxygen saturation (SaO₂) “drops” of ≥5% at least once during the night [24]. In a separate investigation, 12 pregnant women with pre-eclampsia risk factors (including obesity and chronic
hypertension) in the first trimester underwent PSG to identify sleep-related breathing abnormalities and had baseline blood pressure assessments [44]. None of the women had evidence of a clinically significant sleep apnea syndrome. The authors stated that all had significant SDB, as defined by a respiratory disturbance index (RDI) >3 events/h upon initial PSG. However, in pregnant women, inspiratory flow limitation index would be a better indicator of SDB than RDI, because in this population respiratory events may have different characteristics compared with those in patients with UA resistance syndrome (UARS) or OSA [16,45].

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

In a case–control, longitudinal study performed by Edwards et al. [18], women with suspected OSA during late pregnancy were observed to have an AHI of 63±15 events/h and minimum overnight SaO2 of 86%±2%. These measures improved markedly after delivery (AHI 18±4 events/h, SaO2 91%±1%). Interestingly, all of the women in this study

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

AHI: apnea–hypopnea index; BPPV-ST: bi-level positive pressure ventilation in spontaneous/timed modus; CPAP: continuous positive airway pressure; NA: not applicable; NIPPV: nasal intermittent positive pressure ventilation; OSA: obstructive sleep apnea; PIH: pregnancy-induced hypertension; PSG: polysomnography.
were within 15 kg of the highest recommended weight for their height and stage of pregnancy [18].

Earlier data were contributed by Hertz et al., who reported that 12 healthy women had a small but significant reduction in nocturnal SaO2 during the third trimester of pregnancy, compared with that during the post partum period [12]. In another study, arterial oxygen tension (PaO2) measurements in the supine position during sleep were found to be significantly lower during pregnancy compared with during the post partum period [47].

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

Leung et al. performed PSG on eight of 247 pregnant women at 34 weeks’ gestation [25]. None had evidence of significant OSA, and all had a minimum SaO2 of ≥90% during the night. In their study, Brownell et al. also reported that there were no significant changes in oxygenation during sleep between 36 weeks’ gestation and the post partum period, and that the prevalence of apnea and hypopnea was significantly lower during pregnancy compared with after delivery [49]. However, the subjects in these studies were healthy women with no evidence of SDB before the pregnancy. In each study, the investigators used a thermistor to measure respiratory airflow during PSG, which may have led to underestimation of the frequency of obstructive respiratory events [25]. Furthermore, selection bias may have occurred due to the small sample sizes.

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

**Pregnancy-related changes in breathing**

**Changes that increase the risk of SDB**

**Gestational weight and neck circumference**

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

The results of previous studies highlighted that habitual snorers were significantly heavier than non-snorers, before and during pregnancy [2,3,11,23,25,26,46]. Leung et al. found that women with a baseline body mass index (BMI) of >25 kg/m² exhibited a significantly increased frequency of moderate-to-severe snoring intensity compared with those with a BMI of <25 kg/m² [25]. Pien et al. also reported that women with a higher baseline BMI and larger neck circumference during pregnancy reported more symptoms of OSA than others [23]. Additionally, case reports of OSA in pregnancy consistently involve obese women [30,31,38].

Weight gain is a risk factor for developing SDB [38,50–52], especially when associated with increased neck circumference in females [2,23,26,53]. Results from studies of non-pregnant women have also shown that the pharyngeal cross-sectional area and FRC increased with weight loss [50,51,54]. In a study involving the current author, snoring pregnant women had significantly higher pregnancy and pre-pregnancy weight and BMI compared with non-snoring women (by an average of +6 kg and +2 kg/m², respectively) [2]. Snoring pregnant women also had a tendency to have larger neck circumferences, being an average of 1 cm greater than in non-snorers [2]. Additionally, preeclamptic women, who had a high prevalence of SDB, had larger neck circumferences than healthy pregnant and non-pregnant women (by an average of +1 cm and +2 cm, respectively) [26]. In a recent cross-sectional study, neck circumference was also found to be an independent risk factor for PIH, including preeclampsia [11].

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

**Changes in the UA**

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

Nasal obstruction is common during pregnancy. Increased blood and interstitial fluid volumes, and rhinitis of pregnancy (which occurs in 27–42% of women during pregnancy), are possible contributory factors [28]. Increased nasopharyngeal resistance may make airway pressure more negative during inspiration, and contribute to the collapse of the pharyngeal airway during sleep.
Elevated ventilatory drive as a result of increases in progesterone level may induce obstructive SDB by increasing diaphragmatic effort, leading to more-negative inspiratory pressures in the UA [56]. In turn, this may increase the tendency for the airway to collapse during sleep.

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

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

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

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

Hyperventilation occurs due to increased progesterone levels. Minute ventilation is elevated by about 50% during pregnancy, accompanied by a 70% increase in alveolar ventilation [62,65]. Minute ventilation increases can overcompensate for the increased metabolic requirements of pregnancy, thus leading to respiratory alkalosis with a lower partial pressure of carbon dioxide (PCO₂) and a higher partial pressure of oxygen than normal [62,64]. Decreased arterial carbon dioxide tension (PaCO₂) during pregnancy could potentially induce periodic breathing at sleep onset, which has been shown to contribute to SDB [63,66]. These changes may result in respiratory instability and episodes of central sleep apnea during non-REM sleep [63,66].

Changes that reduce the risk of SDB
There are some factors that potentially might decrease the likelihood of oxygen desaturation and SDB during pregnancy. For example, high levels of progesterone will tend to cause hyperventilation, thus reducing PCO₂ at the central chemoreceptors [67,68] and tending to protect UA patency by increasing UA dilator muscle activity [69]. However, this might also cause airway narrowing, as mentioned above.

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

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

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

Maternal complications
PIH is a generic term defined as repeated blood pressure recordings of >140/90 mmHg, first diagnosed after 20 weeks’ gestation in previously normotensive women. If it is not accompanied by proteinuria, this condition is called gestational hypertension, but if it is, it is called preeclampsia [16,26,44,63,73]. A characteristic of hypertension normally associated with preeclampsia is the absence of the usual nocturnal dip in blood pressure, or a decrease in the day–night blood pressure difference, which is similar to the “non-dipper” pattern in OSA [16].
Franklin et al. showed that 14% and 10% of the women who snored habitually had PIH and preeclampsia, respectively, compared with 6% and 4% of non-frequent snorers [3]. Ursavas et al. also reported that 20% and 10.9% of pregnant women with habitual snoring developed PIH and preeclampsia, respectively, compared with 11% and 5.8% of non-snoring pregnant women [11]. However, it is not possible to draw any conclusions regarding cause and effect due to the cross-sectional designs of these questionnaire studies [3].

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

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

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

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

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

Fetal complications

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

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

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

In their study, Franklin et al. reported that habitual snorers were more than twice as likely as non-snorers to give birth to an infant with intrauterine growth retardation or with an Apgar score of <7 at both 1 min and 5 min [3]. After adjustment for maternal age, weight, and smoking habits, differences remained significant and the odds ratio for association with frequent snoring was 3.5 (95% confidence interval 1.3–9.4) for intrauterine growth retardation [3]. However, these findings were obtained from retrospective data, and recollection of symptoms may have biased the results.
Conversely, Loube et al. reported that birth weight, Apgar score, and incidence of perinatal complications were not significantly different between the infants of women with and without regular snoring in the second or third trimester of pregnancy [22]. Likewise, Hedman et al. reported that there was not a significant relationship between snoring and infant birth weight in a prospective survey of sleep symptoms [6]; however, 52% of the subjects could not be followed up in this study.

**Practical aspects of SDB in pregnancy**

**Assessment of symptoms**

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

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

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

As mentioned, women with preeclampsia, even in the absence of OSA, have narrower UAs and higher incidence of inspiratory flow limitation than women with healthy pregnancies [16,26,45]. These women, and those with diabetes or a history of active or passive smoking may be
closely evaluated for the presence of SDB [72]. Women with preeclampsia do not necessarily demonstrate more sleepiness than healthy pregnant women [1]. Thus, in the clinical setting, questions should extend beyond simply asking about a patient’s sleepiness, and should instead focus on other symptoms of SDB. If SDB is present, blood pressure and blood glucose levels should be closely monitored.

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

Prevention of SDB during pregnancy

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

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

Treatment of SDB

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

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

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

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

CPAP pressure may require readjustment due to moderate worsening of SDB as a result of uterine enlargement and fetal growth during pregnancy. For example, in a study of 12 pregnant women diagnosed with SDB in early pregnancy, six needed an increase in CPAP pressure after 6 months' gestation [55]. Adherence to CPAP treatment was very good, at >80%. Home monitoring during the 8th month of gestation demonstrated normal SaO2 during sleep and the absence of apnea, hypopnea, and tachypnea [55].

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

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

Two recent studies by Guilleminault et al. and Poyares et al. evaluated the potential benefit of nasal CPAP usage in pregnant women with preeclampsia risk factors early in pregnancy [44,82]. In a prospective, longitudinal study, 12 women with either chronic hypertension or obesity were recruited in their first trimester and used CPAP throughout pregnancy [44]. Women with chronic hypertension did not develop preeclampsia and did not need to increase their...
dosage of antihypertensive medication, but one of the obese women had preeclampsia. Nasal CPAP was well-tolerated in all hypertensive women, and nightly compliance with CPAP usage was good. CPAP re-titration was required in all subjects [44]. In a randomized, controlled trial of women with chronic hypertension and snoring, nasal CPAP usage combined with standard prenatal care during the first 8 weeks of pregnancy provided better blood pressure control and improved pregnancy outcomes, compared with standard prenatal care alone [82]. None of the women in the CPAP group (n=7) developed preeclampsia, but one of the control subjects (n=9) did [82]. Even though these two studies had certain limitations, such as small sample sizes, the results are promising.

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

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

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

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

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

Disclosures
The author has no relevant financial relationships to disclose.
Acknowledgment
The author would like to thank to Professor Neil Douglas for his valuable advice, support, and encouragement.

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Attention deficit hyperactivity disorder (ADHD) is a common childhood neurobehavioral disorder, with an estimated prevalence rate of 5–10% in the childhood population [1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), ADHD is characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity, with onset before the age of 7 years and impaired functioning in two or more settings (e.g. at school and at home) [2,3]. Although the exact mechanisms underlying the condition have not been fully elucidated, genetic, neurobiological, and environmental factors leading to cerebral dopamine dysfunctions are often reported in the context of ADHD pathophysiology [3,4]. It has been suggested that the cerebral structures concerned (including the prefrontal cortex and frontal lobe, which are associated with attention, and the caudate nucleus and globus pallidus regions, which are involved with motor activity [5]) are potentially related to the dysregulation of arousal mechanisms, and likewise to instability of the sleep–wake balance [6].

In this context, researchers have sought potential links between sleep–wake disorders and the symptoms of ADHD [7]. Using subjective and objective measures, several groups have attempted to clarify relationships between ADHD and sleep disorders [8–11]. The following sleep-related symptoms are most frequently observed in children with ADHD [11]:

- Difficulty falling asleep.
- Bedtime resistance.
- Night awakenings.
- Restless sleep.
- Difficulty awakening in the morning.

This review aims to provide a summary of the current evidence regarding the relationship between ADHD and sleep disorders, and the implications of these findings for the practicing clinician. A number of sleep conditions are considered in turn, along with evidence of the outcomes following different therapeutic strategies. Furthermore, the article considers the effects of comorbid psychiatric conditions and ADHD treatments on sleep.

**Sleep disorders in ADHD: the rationale for investigation**

In the 1950s, Laufer and Denhoff reported that sleep disturbances could represent a significant source of distress for children with ADHD and their parents, stating that: “Generally, the parents of hyperkinetic children are so desperate over the night problems that the daytime ones pale in significance” [12]. Furthermore, in 1973, Wender speculated that the children with “minimal brain dysfunction” (what is now known as ADHD) had “an increased frequency of sleep difficulties: difficulty in falling asleep...”
symptomatology. Bearing this possibility in mind, the increased nocturnal activity contributes to its daytime “24-h” disorder, and that sleep disruption caused by conceivable that, at least in some children, the condition is a ADHD is purely a result of sleep disturbance, but it is not seem indicative of specific sleep disturbances [24], there remain inconclusive, and difficulties in sleep maintenance, low sleep efficiency, and alterations in sleep architecture do not seem indicative of specific sleep disturbances [24], there are often reports of sleep-onset delays, increased motor activity, and deficits in alertness [11].

Management of sleep problems may significantly improve the quality of life of children with ADHD, as well as that of their families [14]. Data from some studies suggest that sleep disturbances worsen ADHD symptoms, associated mood disorders, or both [15,16]; therefore, the treatment of comorbid sleep disorders, and interventions targeted at ensuring adequate sleep, may substantially improve daytime ADHD symptoms [11].

Diagnosis
Any sleep disorder that results in inadequate sleep duration, fragmented or disrupted sleep, or excessive daytime sleepiness can cause problems with mood, attention, and behavior [11]. Therefore, the symptoms of sleep disturbances may mimic those of ADHD in children incorrectly diagnosed with the condition [11,14,15]. As a consequence, in these individuals, symptoms of inattention, hyperactivity, or impulsivity could be improved or even eliminated upon treatment of the primary sleep disorder.

It has also been noted that sleep problems reported by patients with ADHD are multifactorial [8,14], meaning that they can be ascribed to various underlying factors. The correct identification of such factors, therefore, facilitates appropriate management of sleep disturbances in this population [14,16].

Difficulties in settling to sleep and delayed sleep onset have been investigated in children with ADHD through the use of parental reports or questionnaires [8,14,17–18]. Disruptive night awakenings, caused by abnormal activity during sleep, periodic limb movement (PLM) syndrome, or sleep-disordered breathing (SDB) have been reported in studies utilizing actigraphy, video monitoring, and polysomnography (PSG) [18–23]. In cases of ADHD where the results from a number of PSG tests or other objective studies remain inconclusive, and difficulties in sleep maintenance, low sleep efficiency, and alterations in sleep architecture do not seem indicative of specific sleep disturbances [24], there are often reports of sleep-onset delays, increased motor activity, and deficits in alertness [11].

Importantly, the current article does not suggest that ADHD is purely a result of sleep disturbance, but it is conceivable that, at least in some children, the condition is a “24-h” disorder, and that sleep disruption caused by increased nocturnal activity contributes to its daytime symptomatology. Bearing this possibility in mind, the relationship between sleep disorders and ADHD should be considered by healthcare practitioners as part of the global approach to the management of the condition. For example, the practitioner should screen for clinical sleep problems in those with ADHD by specifically asking questions regarding the major symptoms of sleep disorders (e.g. deficits in alertness, sleep-onset delay, increased nocturnal activity). In the author’s opinion, these screening questions should be asked regardless of the nature of the chief complaint from parents (e.g. bedtime opposition) or from children (e.g. inadequate time asleep).

Restless legs syndrome
Restless legs syndrome (RLS) is characterized by uncomfortable leg sensations with an irresistible urge to move the legs. In adults, these leg sensations are more severe when sitting or lying, are characteristically worse at nighttime, and are partially relieved by movement [25]. As a result of their limited ability to describe the subjective symptoms of the condition, children may report RLS differently from adults [26–28]. Therefore, it is difficult for the general practitioner to diagnose RLS in children. In order to help overcome this problem, the International Restless Legs Syndrome Study Group (IRLSSG) has proposed a set of criteria specific for this population [25].

The relationship between RLS and ADHD was examined in a review of the literature published in 2005 [9]. Several hypotheses have been proposed to explain such an association with ADHD or ADHD-like symptoms. RLS-associated sleep disturbance may cause inattentiveness, moodiness, and “paradoxical overactivity” [29], mimicking symptoms of ADHD. Alternatively, idiopathic ADHD and RLS can be comorbid conditions [9]; individuals with RLS, and some of those with ADHD, might share a common dopamine dysfunction [30,31].

It has been highlighted that the dopamine system has a central role in the pathophysiology of RLS [32,33]. Iron is a cofactor in the biosynthesis of dopamine, and it has been suggested that RLS symptoms could originate directly from a primary dysregulation of iron metabolism in the brain [32,34–39]. Moreover, there is an emerging base of literature regarding iron deficiency in children with restlessness, overactivity, and inattention [40–42]. For Picchietti, the notion that iron deficiency might aggravate or, in some cases, induce RLS, ADHD, or both is a promising concept [43].

In the current author’s clinical experience, RLS symptoms may exacerbate, or cause later onset of the symptoms of ADHD during the lifetime of the child. Moreover, children with RLS can develop bedtime opposition, probably because they associate bedtime with the occurrence of the
unpleasant RLS sensations. Parents may consider this refusal as the expression of a general oppositional attitude, ignoring the real cause of the child’s behavior [11]. Therefore, this sleep disorder can be overlooked in children with ADHD and oppositional behavior. Conversely, it is also possible that ADHD worsens RLS symptoms. For example, Chervin et al. noticed that adults with RLS sometimes report that increased daytime activity worsens their nocturnal discomfort [29], and Wagner et al. found that the characteristics of RLS were more severe in adults with ADHD symptoms than in those without [44]. For all these reasons, RLS should be systematically sought in patients with ADHD or ADHD-like symptoms, and vice versa [9].

### Treatment

With regard to therapeutic strategies for patients with both RLS and ADHD, some interesting case reports have demonstrated the efficacy of low doses of dopaminergic agents (levodopa, pergolide, and ropinirole) in children diagnosed with both conditions who were previously treated unsuccessfully with psychostimulants [45,46]. In one of these, a 7-year-old child with ADHD according to DSM-IV criteria, and RLS meeting IRLSSG criteria, had been treated with methylphenidate (MPH) for 1 year with limited efficacy [46]. After 12 weeks of receiving ferrous sulfate (equivalent to 80 mg/day elemental iron), an improvement in symptoms of ADHD was observed (scores on the Conners Parent Rating Scale and the Conners Teacher Rating Scale decreased from 70 to 30 and from 28 to 21, respectively). However, after 5 months there was a return of excessive motor activity at bedtime, with RLS symptoms. In this child, MPH treatment at the beginning of the afternoon appeared to be less efficacious than the earlier ferrous sulfate treatment, and had no effect on his sleep problems. Therefore, the dopamine agonist ropinirole was co-prescribed. After 1 month, the child’s oppositional behavior disappeared, his attention improved, and he slept well (his scores on the Conners parent and teacher scales were 33 and 20, respectively) [46].

Dopaminergic agents are considered to be first-line treatments for adults with RLS, but are not approved for use in children with RLS. Ongoing double-blind studies should determine whether or not these agents are beneficial for children and adolescents as first-line therapies, or following unsuccessful treatment with psychostimulants. Future research will help in determining whether ADHD and a sleep-onset delay due to increased global nocturnal activity may mask RLS in children, and whether or not the administration of dopaminergic agents improves outcomes in these cases [46].

As alluded to above, iron supplementation has also proved effective in the treatment of ADHD in children with RLS [42]. However, additional investigations are needed to more thoroughly define the role of iron deficiency and supplementation in children with RLS and ADHD [31,41,43].

Regarding the implications of these findings for clinical practice, a history of iron deficiency during infancy or in childhood may prompt the physician to measure serum ferritin levels in those with RLS and ADHD. In documented cases of iron deficiency, especially in preschool-aged and very young children (who cannot benefit from psychostimulant treatment for ADHD), clinical commonsense would suggest initially replenishing iron stores and then re-evaluating progress, before instituting other treatment.

#### Sleep-onset insomnia and delayed sleep phase syndrome

In the author’s clinical experience, the parents of children with ADHD often report difficulty initiating sleep at bedtime. This resistance to go to bed can be significant, but not an obvious marker of opposition or provocation from the child. It may be due to delayed sleep phase syndrome (DSPS), which is experienced by approximately one-third of children with ADHD who are not receiving medication [47]. Furthermore, it has been demonstrated that medication-free children with ADHD and sleep-onset insomnia (SOI) exhibit a delayed evening increase in endogenous melatonin levels [48].

### Treatment

Thus far, one open-label study and two randomized, double-blind, placebo-controlled trials have been conducted to assess the efficacy and tolerability of melatonin for the management of SOI in children with ADHD [48–50].

In the open-label study, the effect on insomnia of melatonin 3 mg given in the evening was investigated in a sample of 24 children with ADHD [48]. The authors reported that immediately after the start of treatment, the children fell asleep significantly earlier than before. The long-term effect, after 3 months, was comparable with the immediate effect observed after 1 week. The major limitation of this study is the open-label design, which does not allow a placebo effect to be ruled out.

In the first randomized, double-blind, placebo-controlled study, the efficacy of sleep hygiene coupled with melatonin treatment for SOI was assessed in a sample of 27 stimulant-treated children with ADHD aged 6–14 years [49]. Children first received a sleep-hygiene intervention and the non-responders were recruited into a 30-day double-blind, randomized, placebo-controlled, crossover trial of melatonin 5 mg. A significant improvement in sleep-onset time was noted with melatonin compared with placebo, but it is not possible to infer whether melatonin would have been effective in the absence of sleep hygiene. Secondly, as there
was no prescreening with PSG, patients with undiagnosed primary sleep disorders may have been enrolled in the study.

The second controlled study assessed the efficacy and tolerability of melatonin (3 mg/day for those with body weight <40 kg, and 6 mg/day for those weighing >40 kg) in 105 medication-free children with ADHD and SOI [50]. Using actigraphy, it was found that sleep onset advanced by 26.9±47.8 min with melatonin, and was delayed by 10.5±37.4 min with placebo (p<0.0001), after 4 weeks of treatment. As in the first controlled study, this investigation did not utilize PSG measurements.

Despite their limitations, the abovementioned studies suggest that melatonin might be an effective treatment for SOI in children with ADHD. However, since data on possible long-term effects, such as those on the gonadotrophic system and the onset of puberty are not available, further evidence is needed before melatonin can be systematically recommended for SOI in children with ADHD.

Considering that a delayed evening increase in endogenous melatonin levels might explain SOI in those with ADHD, some investigators have assessed the effect of light therapy (LT) in this population. In an open trial, Rybak et al. administered 3 weeks of morning bright LT to 29 adults with ADHD [51]. They observed a significant phase advance in circadian preference, as well as an improvement in both subjective and objective measures of ADHD. To the author’s knowledge, no controlled study has been conducted to assess the efficacy of LT in patients with ADHD. Moreover, with the exception of a recent case report [47], no studies have included children.

The findings from these studies suggest that, in some cases, ADHD may be characterized by the SOI element of DSPS. Practitioners should be aware that the amelioration of circadian-phase problems may have a reciprocal beneficial effect on ADHD symptomatology.

**Excessive nocturnal activity**

Previous studies utilizing actigraphy have documented an excessive nocturnal motility in children with ADHD [18,19,29]. In only one study has excessive nocturnal activity in children with ADHD been reported using nocturnal video-monitoring and PSG [52]. In this particular investigation, the sleep patterns of 30 children with ADHD were compared with those of 19 controls. Using video–PSG, the duration of movements was found to be significantly greater in children with ADHD compared with the control individuals (p<0.03 for upper limb movements; p<0.02 for all types of movements). Unfortunately, due to a technical issue, PLMs were not scored.

In a meta-analysis conducted by Cortese et al., it was suggested that the number of movements in sleep is higher in those with ADHD than in controls [9]. Although one might suppose that increased nocturnal activity fragments sleep, leading to sleep disturbance, no significant differences in sleep variables between children with ADHD and controls were observed. Moreover, PSG data were not significantly different between the two groups [9].

These findings suggest that ADHD is not a purely diurnal disorder, but that it also has significant consequences for sleep that require systematic investigation; nocturnal video-monitoring may be of diagnostic assistance.

**Treatment**

Interestingly, it has been reported in children [53] and adults with ADHD [54] that late-afternoon MPH doses reduce nocturnal activity and improve sleep quality by consolidating sleep. However, whereas some studies have showed that MPH three-times daily does not impact upon sleep [55], or causes only a slight decrease in sleep duration [56], others have reported that a third daily dose of MPH does worsen sleep [57].

Given these contrasting findings, late-afternoon stimulant treatment cannot yet be recommended for ADHD patients with high nocturnal activity, and further research to clarify this controversial issue would be welcomed. As stated by Jerome: “It is a common clinical experience of clinicians treating children with ADHD that on occasion a small dose of MPH taken before bedtime can facilitate sleep. Although this is not the case for all children with ADHD it seems to be a robust clinical finding, which is not well documented in the literature” [58].

In summary, very few studies have assessed the treatment of increased nocturnal activity with evening administration of MPH, but these findings may have important clinical and therapeutic implications for children with this symptom.

**PLMs in sleep**

PLM disorder (PLMD) is a nocturnal condition characterized by the presence of brief jerks of the limbs during sleep, which [59–61]:

- Occur in series of four or more, with each movement lasting 0.5–5 s.
- Have an amplitude of at least one-quarter of the toe dorsiflexion during calibration.
- Are separated by intervals of 5–90 s.

The diagnosis of PLMD is determined by PSG, which includes electroencephalography, electro-oculography, submental electromyography (EMG), and bilateral EMG of the *tibialis anterior* muscles. PLMD is described as rhythmic extensions of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip [59–61].
PLMs in sleep (PLMS) have also been described in children. However, the clinical presentation differs from that of adults in that children with PLMS may present with non-specific symptoms, such as growing pains, restless sleep, insomnia, or excessive daytime sleepiness, but most often these issues go unnoticed by their parents [27,62,63] even though a family history of RLS or PLMS is common [63,64].

In a series of studies, Picchietti et al. suggested a heightened prevalence of PLMS among children with ADHD [20,63,65]. The prevalence of PLMS in the general pediatric population is low [66,67], but it may increase to 64% in children with ADHD [68]. In two studies, between 26% and 64% of children with ADHD had >5 PLMs/h of sleep [20,69]. In the first of these, where 69 children and adolescents (aged 2–16 years) with ADHD were studied, eight of 18 (44.4%) participants with >5 PLMs/h also had a positive parental and personal history of RLS [20].

In the second investigation, six of nine (32%) children with ADHD and >5 PLMs/h had a positive parental history of RLS [69]. It seems that not only do children with ADHD more often have PLMS than those without ADHD, but children with PLMS are also more likely to have ADHD; approximately 44% of children with PLMS may have symptoms of ADHD [70].

From these compelling findings, it is suggested that RLS and PLMS, either separately or in combination, occur more frequently in those with ADHD, and vice versa [31].

Treatment

Guidance from the Standards of Practice Committee of the American Academy of Sleep Medicine states that no specific recommendation can be made regarding treatment of children with RLS or PLMS [62]. Furthermore, there is limited information available on the use of dopaminergic medications in children [71]. The investigators of some studies on the dopaminergic agonists pramipexole and ropinirole reported beneficial effects on PLM symptoms in children with ADHD and PLMS [46,72]. Upon treatment with pramipexole, Guilleminault et al. described, in two adolescents with RLS and PLMD, an improvement in the PLM arousal index, with decreases from 11 and 16 arousals/h to 0 and 0.2 arousals/h, respectively [72].

As discussed above for RLS, another interesting observation spurred by the relationship between PLMS and ADHD in children, concerns iron status. Children with PLMS or RLS may have iron deficiency, as evidenced by low serum ferritin and iron concentrations [73,74]. In a study by Simakajornboon et al., 28 of 39 (71.8%) children with PLMS, aged 1–13 years, had a serum ferritin level of <50 μg/L. Out of these 28 children, 25 received treatment with iron sulfate (equivalent to elemental iron 3 mg/kg/day), and 19 (76%) responded favorably. Almost all patients with PLMS and ADHD (n=16) had ferritin levels of <50 μg/L; 14 received treatment with iron sulfate, and 12 of these (85.7%) responded favorably to the therapy, with the PLM index decreasing from 31.6±17.4 PLMs/h to 15.4±5.4 PLMs/h after 3 months [74]. This improvement suggests that it would be worthwhile to conduct a randomized, placebo-controlled trial of this therapy for PLMS.

Based on the role of iron in the pathophysiology of RLS and PLMS, it can be postulated that iron deficiency could lead to alterations in dopaminergic pathways and neurotransmission; therefore, iron deficiency may affect PLMS severity. As a result, practitioners should be aware of the possibility that iron therapy, in some cases, may lead to clinical improvement in PLMS.

SDB

The relationship between SDB and ADHD is still speculative. The results of several studies have demonstrated an association between symptoms of SDB and ADHD [75,76]. However, as some of these investigations did not employ standardized ADHD criteria, it is not clear whether SDB is linked with ADHD symptoms or “full” ADHD (i.e. that diagnosed according to these criteria). That said, a meta-analysis, which included studies utilizing rigorous criteria for ADHD, suggested that mild SDB may indeed be associated with full ADHD [10].

Treatment

With regard to treatment strategies in this population, Huang et al. conducted a controlled study of 66 children with ADHD and an apnea-hypopnea index of >1 to <5 events/h [77]. Of this group, 27 children were treated with MPH for ADHD, 25 had adenotonsillectomy for SDB, and 14 had no treatment. Children in the surgical intervention and MPH groups improved more than those who received no treatment. Furthermore, when comparing outcomes in the surgical intervention and MPH groups, there was a significant difference in sleep disturbance measured on a questionnaire. Moreover, some daytime symptoms (including attention span) and results from subscales of the Test of Variables of Attention (impulse control, response time, and total ADHD score) improved to a greater extent in those who had been treated surgically compared with those receiving MPH [77].

These promising results should prompt further studies to assess the effectiveness of surgery in patients with SDB and ADHD, for the treatment of both sleep disturbance and core ADHD symptoms. They also suggest that appropriate recognition and surgical treatment of underlying SDB in children with ADHD might prevent long-term stimulant treatment [75–77].
Excessive daytime sleepiness
Children with ADHD may have a deficit in alertness. Primarily, it has been hypothesized that excessive motor activity could be a strategy used by ADHD children to stay awake and alert [78]. Subjective questionnaires completed by parents may not be suitable to assess sleepiness, which could be masked by hyperactivity. Instead, the Multiple Sleep Latency Test (MSLT) is considered the “gold standard” method for assessing alertness. The results of two studies employing the MSLT have confirmed excessive daytime sleepiness in children with ADHD [78,79].

In the first study, of 30 boys aged 5–10 years with ADHD, and 22 age- and sex-matched controls, Lecendreux et al. reported shorter sleep-onset latency for patients with ADHD in naps one, two, and three using the MSLT [78]. The number and duration of sleep onsets were correlated significantly with hyperactivity–impulsivity and inattentive–passivity scores. None of these differences could be attributed to any differences in nocturnal sleep. Thus, an accurate validation of the MSLT methodology in children could further support the notion of a hypoarousal state in ADHD children [78]. In the second study, 34 children with ADHD (mean age 12.4 years) were significantly more drowsy compared with controls, as measured with the MSLT (p<0.05) [79].

However, according to the findings of one study, up to one-third of adults with ADHD may have subjective sleepiness (a score of >12 on the Epworth Sleepiness Scale) [80]. In this investigation, inattention scores were correlated with the excessive daytime sleepiness values.

In summary, drowsiness is common in ADHD. Questionnaires designed to investigate sleep and alertness specifically in school-aged children and adolescents should be developed, as these individuals can provide a more reliable description of some sleep disturbances than their parents. Moreover, in those with excessive subjective sleepiness, somnolence should be assessed objectively.

Treatment
These findings suggest new potential therapeutic strategies for a subgroup of children who present with ADHD associated with an alteration in sleep or wakefulness, and who may not respond adequately to first-line stimulant treatments, such as MPH and amphetamine salts. Wake-promoting agents, although presently overlooked in this population, could be an important alternative to stimulants in those children with ADHD who present with a subjective complaint of daytime somnolence confirmed by short, but not excessive, mean sleep latencies according to the MSLT [78,79]. The use of the wake-promoting, non-stimulant agent modafinil has been proposed for this specific indication, although the drug is not yet approved for use in this way [81,82]. Once the efficacy and tolerance of modafinil in children have been proven, further double-blind studies should be conducted to evaluate the potential usefulness of this agent specifically in children with ADHD.

This author suggests that future research should seek to improve the assessment of potential specific patterns of sleep or alertness disturbances in children with ADHD and, consequently, define more appropriate treatment applications.

Sleep, ADHD, and psychiatric comorbidities
Psychiatric comorbid disorders are relatively frequent in ADHD, probably being present in as many as two-thirds of clinically referred children with the condition; examples include oppositional disorder (present in up to 50% of patients), conduct disorder (30–50%), mood disorders (15–20%), anxiety disorders (20–25%), learning disorders (10–25%), developmental coordination disorder (>25%), and tic disorders (approximately 20%) [83–87]. Moreover, Tourette’s syndrome and, in adolescents, substance abuse may also be comorbid with ADHD [88]. All of these psychiatric disorders might be associated with significant sleep disturbances [89]. As an example, in the case of Tourette’s syndrome, available data suggest that the condition is associated with disturbances including:

- Longer sleep period time.
- Longer sleep latency.
- Reduced sleep efficiency.
- Prolonged wakefulness after sleep onset [88].

In considering the impact of psychiatric comorbidities on sleep, the author suggests that there is a need to systematically evaluate these in patients with ADHD, especially when sleep problems are reported. Clearly, the appropriate treatment of comorbid disorders may improve sleep, but the clinician should keep in mind that some medications used to treat these conditions may negatively impact upon sleep (e.g. selective serotonin reuptake inhibitors).

Pharmacological treatment of ADHD and sleep disturbances
It has been suggested that stimulants used in the pharmacological treatment of ADHD lead to sleep disturbances when sleep alterations are not screened for before medication administration. Psychostimulants (MPH, amphetamine, lisdexamfetamine dimesylate) are the first-line, US Food and Drug Administration-approved treatments for ADHD, followed by the non-stimulant atomoxetine (ATX). However, non-approved drugs, such as bupropion, tricyclic antidepressants, α-agonists, and modafinil, are also used [90].
Psychostimulants
Subjective and objective studies investigating the effects of stimulants on sleep have produced mixed results [91]. While some investigators have reported, among other outcomes, lengthened total sleep time, increased sleep-stage shifts, increased number of rapid eye movement (REM) sleep periods, elevated indices of REM activity, and REM-period fragmentation, others did not confirm these findings [10,91]. It is difficult to assimilate the results of these studies because of the different stimulants, formulations, doses, and dose-scheduling protocols used.

As stimulant use may be associated with the so-called “rebound effect” [92], whereby behavior deteriorates as the effect of the drug wears off, it is possible that reported sleep problems may be linked with such restlessness rather than occurring as a direct action of the agents themselves. However, the investigators of studies employing a third daily dose of stimulant (to avoid the rebound effect) did indeed observe a more significant sleep-onset delay in children treated with stimulants compared with untreated subjects [93,94].

Considering this evidence, and also on the basis of clinical experience, it is possible to conclude that stimulants may negatively impact upon sleep, due either to a direct or to a secondary “rebound” effect. Vulnerability to these negative effects is likely to be related to individual factors. As highlighted by Brown and McMullen, while some patients with ADHD are able to get to sleep easily within just a few hours of taking a dose of stimulant, others need an interval of 6–8 h [95].

ATX
Regarding the effect of ATX on sleep in children with ADHD, in a recent randomized, double-blind, crossover study comparing the effect of MPH given thrice daily and ATX given twice daily, Sangal et al. found that MPH increased sleep-onset latency significantly more than did ATX, considering both actigraphic and PSG data [91]. Moreover, both child diary entries and parental reports indicated a better quality of sleep with ATX compared with methylphenidate. Both medications decreased nighttime awakenings, but the decrease was greater with MPH [91]. Clearly, these results need to be replicated in additional studies.

Practical implications
On the basis of the abovementioned effects of ADHD medications on sleep, a panel of ADHD experts proposed a number of strategies to manage sleep alterations caused by stimulant use (Table 1) [96]. If the impact of these treatments upon sleep is caused by a “rebound effect,” in the current author’s clinical experience, giving a low dose of MPH in the late afternoon or evening could be helpful. Doses in late evening could also be considered if the rebound effect persists. As noted >30 years ago by Kinsbourne, “if a hyperactive child wakes during the night, giving him a stimulant should help him go back to sleep” [97].

It is important to note that these suggestions are not intended as guidelines and, at the present time, given the paucity of controlled studies, no evidenced-based recommendations can be made. Regarding clonidine in particular, while no controlled study results are available, a systematic chart review of 62 children and adolescents with ADHD, who were treated with the drug for their sleep disturbances, found that clonidine may be useful in managing sleep problems in children with ADHD. However, the exact mechanism by which clonidine affects sleep is not fully understood.

Table 1. Pharmacological strategies in children with attention deficit hyperactivity disorder and sleep alterations.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simply wait</td>
<td>Generally insomnia caused by stimulants attenuates after 1–2 months</td>
</tr>
<tr>
<td>Adjust dose or dosing schedules</td>
<td>Adjust dose or avoid evening stimulant dose</td>
</tr>
<tr>
<td>Switch to another stimulant formulation</td>
<td>Different formulations of the same stimulant may impact differently upon sleep</td>
</tr>
<tr>
<td>Switch to a non-stimulant</td>
<td>Some data suggest that amphetamines have a greater impact on sleep than stimulants</td>
</tr>
<tr>
<td>Add antihistamines</td>
<td>Trazodone, mirtazapine, or better, melatonin</td>
</tr>
<tr>
<td>Use clonidine</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Kratochvil et al. [96].

Table 2. Author’s key messages regarding ADHD and sleep disturbances.

<table>
<thead>
<tr>
<th>Message</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study results</td>
<td>Confirmed the relationship between ADHD and sleep disorders</td>
</tr>
<tr>
<td>Prior research findings</td>
<td>Children with iron deficiency can develop sleep disorders such as RLS or PLMS</td>
</tr>
<tr>
<td>Positive familial history</td>
<td>May enhance the risk of children with ADHD developing RLS and PLMS</td>
</tr>
<tr>
<td>Sleep-onset delay</td>
<td>Is not obviously a symptom of opposition to sleep in children with ADHD</td>
</tr>
<tr>
<td>Sleepiness or drowsiness</td>
<td>Is commonly reported in children with ADHD with predominant inattention</td>
</tr>
<tr>
<td>Whether or not ADHD symptoms</td>
<td>More common in patients with, rather than without, DSPS remains to be explored</td>
</tr>
</tbody>
</table>

ADHD: attention deficit hyperactivity disorder; DSPS: delayed sleep phase syndrome; PLMS: periodic limb movements in sleep; RLS: restless legs syndrome.
disturbances, highlighted that 85% were considered to be much-to-very-much improved, according to the US National Institute of Mental Health global assessment of improvement [98]. Adverse effects attributable to clonidine treatment were generally mild and occurred in 31% of patients. The most common adverse effect included morning sedation and fatigue. Interestingly, although inadequate data were available to assess vital signs and electrocardiogram results systematically, there were no clinical symptoms referable to hypotension or arrhythmia [98].

Conclusion

The relationship between sleep disorders and ADHD is strongly documented within an increasing literature base, albeit at a time when there is a lack of consensus regarding the pharmacological management of sleep problems. This review of the literature has detailed specific clinically and polysomnographically determined diagnoses of the sleep disturbances most evidently linked with ADHD, and the author’s key messages are listed in Table 2.

It has recently been appreciated that RLS and PLMS may occur in childhood, and may frequently arise in children with ADHD. The initial interest in this area resulted from pathophysiological, pharmacological, and PSG studies, which established a possible association between ADHD, restlessness, and motor activity during sleep.

Looking ahead, the interesting issue of the relationship between ADHD and narcolepsy or primary disorders of vigilance has yet to be fully explored. In a recent meta-analysis, it was concluded that subjects with ADHD present with higher daytime sleepiness than controls [10]. The findings of a pathophysiological relationship between ADHD and these conditions would suggest a need to study the effectiveness of wake-promoting agents for patients with ADHD and excessive daytime sleepiness.

Disclosures

The author has no relevant financial relationships to disclose.

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References

Impact of Insomnia: Wide-Reaching Burden and a Conceptual Framework for Comorbidity

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Insomnia presents a significant burden in a number of senses, as it is associated with a decline in quality of life, an increased rate of accidents, absenteeism, direct and indirect economic costs, and subjective discomfort. This article describes such associations, and focuses on another kind of burden, that of insomnia interacting with other medical and psychiatric illnesses. Recent years have seen a change in the emphasis of insomnia research, from a focus on primary insomnia to one on sleep disturbance presenting in combination with other illnesses, which is indeed the most common way that insomnia appears in medical practice. Several studies have suggested that treatment of comorbid insomnia may improve the symptoms of some accompanying illnesses, signifying an interactive process. Insomnia has also been shown to be a risk factor for a number of conditions; however, as a risk factor it might, in principle, have several different kinds of association with a second illness. These possibilities are considered in turn, using major depressive disorder as a model of a comorbid condition, and a conceptual framework for considering these relationships is proposed as an aid to future study design. Int J Sleep Wakefulness 2008;1(3):118–23.

The last decade has seen the publication of a variety of articles indicating that the burden of insomnia reaches far beyond the subjective suffering of the patient, extending into many aspects of his or her daytime waking life (e.g. [1–4]). Insomnia has been found to be associated with decreased quality of life and productivity, as well as increased absenteeism from work, accidents, and general healthcare utilization. It has also been identified as a risk factor for the subsequent development of other conditions, such as major depression, generalized anxiety disorder, and coronary artery disease (e.g. [5,6]).

The interaction of insomnia with coexistent medical and psychiatric conditions represents another type of burden; given that the most common clinical presentation of insomnia is in the context of another illness, this is of particular significance. Indeed, there has been a sea change in the way that most sleep researchers view insomnia coexistent with a second disorder, largely as a result of observations that treating sleep disturbance can not only relieve insomnia-associated suffering but also ameliorate the symptoms of some accompanying illnesses (e.g. [7]). Such observations have led to a name change, from the traditional “secondary insomnia” to the newer “comorbid insomnia,” with the latter emphasizing the interactive nature of the two processes [8]. Beyond stating that there appears to be an interaction, very little has been published regarding what these studies might imply about the nature of the basic relationship between insomnia and an accompanying illness. This article will review some of the study results, and then propose a possible conceptual framework on which this association can be considered. The studies cited were chosen for their illustrative value, rather than in an effort to provide a comprehensive literature review.

The wide-reaching burden of insomnia

Employment

One of the earliest studies suggesting that insomnia affects a person’s daytime life came from a population of US Navy recruits. Johnson and Spinweber reported in 1983 that those who described having sleep disturbance during their intake examination generally did more poorly in their service [9]. Beyond stating that there appears to be an interaction, very little has been published regarding what these studies might imply about the nature of the basic relationship between insomnia and an accompanying illness. This article will review some of the study results, and then propose a possible conceptual framework on which this association can be considered. The studies cited were chosen for their illustrative value, rather than in an effort to provide a comprehensive literature review.
A decade later, the current author explored whether a similar phenomenon might occur in civilian populations [10]. A questionnaire regarding sleep habits was given to 392 workers at a large international bank at the time of their pre-employment medical examination, between March 1991 and August 1992. It was found that 17.1% of the workers described chronic sleep disturbance, and of this proportion only 10.4% had ever taken a hypnotic. Owing to the possibility that insomnia might have differential effects depending on the type of work performed, subjects were divided into officers (n=174) and non-officers (n=218). At the time of follow-up (after a mean period of 28 months), 93.0% of officers and 77.1% of non-officers were still employed at the bank. Among officers who were still employed there, 16.8% had described poor sleep during their pre-employment examination; of those no longer employed there, 41.7% had described poor sleep (p<0.03). The corresponding values in the non-officers were 14.3% and 22.8%; this latter difference was not statistically significant. Thus, among the officers, those who were no longer employed after approximately 2 years were more than twice as likely to have initially reported poor sleep, compared with those still employed at the bank [10].

Most, but not all, studies have shown increased absenteeism among those with insomnia (an example of an exception is the study reported in [3]). When comparing 369 pairs of insomniac patients and good sleepers, Leger et al. found that those with insomnia were twice as likely to miss work [1]. They also had a higher rate of traffic accidents, and a threefold-higher likelihood of having had two or three serious traffic accidents.

Quality of life
The ramifications of insomnia on an individual’s daytime life appear to reach considerably beyond work, with evidence suggesting that the condition affects overall quality of life. A study of French employees, for instance, found that those who self-reported insomnia had significantly lower scores in the Nottingham Health Profile categories of social isolation, energy, emotional reaction, and physical mobility [3]. Furthermore, Zammit et al. reported that insomniac patients rate more poorly on the 36-item Short-Form Health Survey (a health-related quality of life measure) compared with healthy controls [2]. Among the scales on which these patients demonstrated deficits were social functioning, physical functioning, vitality, and mental health [2]. In another study employing the same measure, insomniac patients were found to have more deficits than those with major depression or congestive heart failure on scales including general health and vitality [11].

Healthcare utilization
Insofar as insomniac patients rate their health and vitality lower than others, it is not surprising that they also utilize the healthcare system to a greater extent. Hatoum et al. studied 1100 randomly selected primary care patients in five large clinics, and found that approximately one-third reported having insomnia that they believed affected their daytime lives [4]. After controlling for comorbid illness and demographic differences, those with insomnia were found to use the healthcare system significantly more frequently than control subjects during an 8-week period. Among the measures on which insomnia was shown to have an effect were the number of visits and phone calls to physicians, the number of emergency room visits, and laboratory test results, as well as the likelihood of receiving any prescription or taking an over-the-counter drug [4].

Simon and VonKorff conducted face-to-face interviews with 373 primary care patients in a staff-model health maintenance organization, and found that patients with insomnia had more health-related disability and more health service utilization than those without the condition [12]. Adjustment for the coexistence of depression and chronic medical illnesses only partially accounted for these associations, indicating a direct contribution of insomnia itself [12]. Daley et al., in a telephone survey of 2000 adults in Quebec, Canada, similarly found that those with insomnia complaints had a higher rate of healthcare consultations, a greater number of prescriptions, and increased expenditures for prescriptions [13].

As the findings of Daley et al. suggest, the increased healthcare utilization of those with insomnia extends from measures of visits and prescriptions received to include actual dollars spent as well. Ozminkowski et al. recently reviewed the medical claims for approximately 200 000 persons enrolled in a self-insured, employer-sponsored insurance plan [14]. After using propensity score matching for variables such as demographics, health plan type, and comorbidities, it was found that over the course of 6 months, direct and indirect healthcare costs for younger people (aged 18–64 years) with insomnia were US$1253 greater than for control subjects without insomnia. For older people (≥65 years of age) with insomnia, direct and indirect costs were US$1143 greater than those for non-insomniac control participants [14].

Using a similar database (the 1999–2003 Medstat MarketScan® Health and Productivity Management Database [Thomson Healthcare, Ann Arbor, MI, USA], which contains information on 800 000 employees of 10 large corporations across 43 US states), Hawkins et al. identified 5605 persons aged >18 years who had insomnia, as defined by having a medical or hospital claim with a primary diagnosis of
insomnia (codes 307.41, 307.42, 307.49, or 780.52 in the International Classification of Diseases, Ninth Revision, Clinical Modification [15]), or at least one pharmacy claim for a non-benzodiazepine hypnotic medication with an indication for sleep [16]. For all subjects included, this was a first diagnosis; individuals with a diagnosis of insomnia or a prescription for a hypnotic in the previous 6 months were excluded. The remaining non-insomniac employees were randomly assigned an index date, which was based on the date of diagnosis or the date of hypnotic prescription for the insomnia subjects.

From a pool of 55,580 control subjects, a propensity score matching procedure was performed on the basis of a logistic regression analysis of the probability of having insomnia, in order to create a group similar to those with insomnia in terms of demographics as well as morbidity, as determined by the Charlson Comorbidity Index (CCI), the Psychiatric Diagnostic Groups (PDG) measure, and the prevalence of the 10 conditions most commonly comorbid with insomnia. Healthcare claims and indirect costs due to absenteeism from work were determined for both groups over the course of the 6 months prior to the index date. It was found that the per-individual costs for the insomniac patients exceeded those of the non-insomniac participants by US$2738 (p<0.001). Healthcare costs comprised 84% of this figure, while absenteeism costs accounted for only 16%. Since these groups were matched for their degree of illness and impairment, this figure represents the unique burden of insomnia [16].

Insomnia treatment
The study results described above highlight the widespread implications of insomnia for medical care. Thus, it is worthwhile considering the treatment of insomnia and its potential effects on this appreciable burden. For example, what happens to healthcare utilization and the outcome of comorbid conditions when insomnia is treated?

Effects on healthcare utilization
The recent study by Hawkins et al. discussed earlier indicated that the direct and indirect healthcare costs of insomniac patients in the 6 months prior to diagnosis exceeded those of propensity score-matched controls [16]. In an extension of that study, the investigators measured healthcare costs for the 6-month period after the index date (the date of first diagnosis or first prescription of a non-benzodiazepine hypnotic), in order to determine if they were affected by therapeutic intervention.

To this end, patients with insomnia were divided into two groups: those who received a prescription for a non-benzodiazepine hypnotic during the 14 days following the index date (the “treated” group; n=4798), and those who did not (the “untreated” group; n=786). Differences were noted between the two groups in the pre-index period. Compared with the untreated group, the treated participants were slightly older (aged 40.79±8.94 years vs. 42.74±8.63 years, respectively; p<0.0001) and had a higher burden of comorbid conditions (CCI scores 0.11±0.48 vs. 0.34±1.08, respectively; p<0.0001). Similarly, the treated group had a higher burden of psychiatric illness than the untreated participants (PDG scores 0.27±0.59 vs. 0.19±0.49, respectively; p<0.0001). They also had higher rates of several common disorders, including essential hypertension, mechanical lower back disorder, and bipolar illness [16].

An ordinary least squares regression analysis was used to compare the change in total expenditures (i.e. post-index costs minus pre-index expense) between treated and untreated insomnia patients, and control subjects who did not suffer from insomnia. It was found that total per-individual expenditures significantly increased by US$1280 between the pre- and post-index periods for untreated insomnia patients (p<0.0057). In contrast, an increase in expenditures between the pre- and post-index periods of only US$492 was observed for treated insomnia patients (p=0.0385). Thus, a comparative saving of US$788 (US$1280 minus US$492) over the 6-month post-index period was observed for those treated for insomnia; this between-group difference was statistically significant (p<0.038) [16].

The lower increase in healthcare costs for the treated patients is even more striking considering that, in comparison, the untreated insomnia group was younger and healthier. The primary cost drivers in the 6 months after diagnosis were healthcare costs that were not specific to insomnia [16].

Effects on comorbid illness
As highlighted earlier, insomnia commonly presents clinically in the context of a comorbid illness, and the interaction between the two conditions represents an additional burden. What effect does treating insomnia have on the outcomes of coexistent conditions? The present author’s view is that, due to the varying methodologies and qualities of the studies conducted to date, combined with the limited number of treatments employed, it may be too early to generalize. However, several studies (outlined below) have suggested that insomnia treatment has benefits for the comorbid condition in several individual disorders, including major depression, generalized anxiety disorder (GAD), and rheumatoid arthritis (RA).

This is an important area of study, as the notion of amelioration of a comorbid condition through the treatment
of insomnia is a cornerstone in the recent change to viewing insomnia as “comorbid,” rather than as “secondary” to another condition.

Articles describing the use of hypnotics are cited herein to illustrate these points; however, the reader should be aware that some research has been undertaken with other therapies (as described in [17,18]). Furthermore, while the potential benefits of hypnotics in this context are discussed below, as with any pharmacological agent, the risks associated with treatment should also be considered by practitioners.

**Depression**

Perhaps the most often-cited study in this area is that of Fava et al., who examined the effects of nightly administration of eszopiclone 3 mg or placebo to 545 patients who were receiving fluoxetine in the mornings for major depression [7]. It was found that those who received combination eszopiclone–fluoxetine therapy had a significantly greater improvement in scores on the Hamilton Rating Scale for Depression (HAM-D) in the 4th week of treatment, and continued to progress favorably until week 8. Their Clinical Global Impression Severity scores also improved significantly during weeks 2–8 compared with those of the fluoxetine–placebo group, and there were significantly more responders to antidepressant therapy overall (59% vs. 48%). Thus, the Fava et al. study suggested that the effectiveness of antidepressant treatment was greater when a hypnotic was administered to deal with the sleep disturbance [7].

In contrast, a study by Asnis et al. did not note this effect [19]. In their 4-week study, in which either zolpidem 10 mg or placebo was given to 190 depressed patients receiving selective serotonin reuptake inhibitor (SSRI) treatment, there were improvements in various measures of sleep and daytime alertness and concentration, but no significant changes in scores on the HAM-D or results from clinical assessments [19]. The Fava et al. and Asnis et al. studies differed in several ways, including choice of hypnotic and SSRI, and duration of administration, so direct comparison of results is not feasible. However, it seems safe to say that additional studies will be needed before more firm conclusions can be made regarding the interaction of insomnia treatment and depression.

**Generalized anxiety disorder**

As another example of a comorbid condition, Pollack et al. recently studied 595 patients with GAD and sleep disturbance who were being treated with escitalopram 10 mg/day, and who were then randomized to also receive either eszopiclone 3 mg/day or placebo for 8 weeks [20]. It was found that a favorable response (defined as a 50% reduction in the Hamilton Rating Scale for Anxiety [HAM-A] at week 8) occurred significantly more often in the eszopiclone group (62%) than in those taking placebo (49%), and that scores on the HAM-A were closely associated with response on the Insomnia Severity Index. Similarly, concurrent remission of both insomnia and anxiety was significantly more common in the eszopiclone group [20].

**Rheumatoid arthritis**

In the preceding sections, depression and GAD were used as models of the interaction of insomnia with a comorbid psychiatric illness. In an analogous manner, RA can be considered as a model of the interaction between insomnia and a medical illness. Roth et al. studied 153 patients receiving treatment for RA, who were additionally given eszopiclone 3 mg/day or placebo for 4 weeks [21]. As well as an improvement in various sleep measures and daytime alertness and function, scores over the entire treatment period from the interactive voice response system used to assess RA demonstrated benefits in current pain severity, pain severity on the previous day, and ability to function, though not in duration of joint stiffness. At week 4, there was also an improvement in scores on the overall Arthritis Self-Efficacy Scale and in the number of tender joints [21].

The findings of Drewes et al. [22] contrast with these positive results. In that study, 40 RA patients were given zopiclone 7.5 mg/day or placebo for 2 weeks. Patients reported an improvement in subjective sleep measures, but there were no changes in pain or clinical measures.

The data presented by Walsh et al. fall between those provided by the two previous studies in terms of the interaction between sleep and arthritic symptoms [23]. Utilizing a crossover design, 15 RA patients were sequentially given triazolam and placebo for 7 nights each. Compared with placebo treatment, polysomnographically measured total sleep was increased and daytime sleepiness reduced after 1 week of triazolam administration. Morning joint stiffness was also reduced, although there were no changes in clinical arthritis assessments [23]. Differences in medication, methodology, duration, and other variables make it difficult to directly compare the results of these three studies, with the most notable difference perhaps being the longer duration of the analysis performed by Roth et al. [21]. However, it seems possible that treatment of sleep disturbance concomitant with RA may improve some arthritic symptoms. More data, with drugs administered for longer durations, will be needed to clarify this issue.

**A conceptual framework for the relationship between insomnia and comorbid illnesses**

In summary, the previous sections of this article have described the wide-reaching burden of insomnia, and reviewed a
number of studies that, while not conclusive, highlight the possibility that treating insomnia may benefit some comorbid illnesses and alleviate healthcare costs not directly related to insomnia. Regarding comorbid conditions, these findings beg the question of what the relationship might be between the two disorders. Unfortunately, there is little information on this subject in the published literature base.

While the results of several studies indicate reasonably conclusively that insomnia is a risk factor for the subsequent development of depression (e.g. [5,6]), the issue remains that a “risk factor” may relate to an associated condition in a variety of different ways. In the case of depression, insomnia might be an early sign of the condition, a “state marker” as a recent study by Neckelmann et al. suggests [24]. Alternatively, insomnia could be an independent disorder that renders a person more vulnerable to the later development of the second condition; or, insomnia and the comorbid condition might both be consequences of a third factor.

With this in mind, it is worthwhile to briefly speculate on a conceptual framework for the possible relationships between insomnia and a coexisting illness. This may be useful to consider when designing future studies in this field. An example of a comorbid condition that frequently appears with sleep disturbance, the present author has employed major depressive disorder. The four most obvious relationships are listed below.

**Insomnia makes one more vulnerable to a second disorder**
In the case of depression, the implication might be that disturbed sleep has a deleterious effect on subsequent mood regulation. One piece of evidence that might be taken to support the view of increased vulnerability is the observation that the most common temporal association between insomnia and depression is the former preceding the latter [25]. It should be noted, however, that insomnia occurred at the same time or later than the mood disorder in 60% of cases in this study, suggesting that the relationships between the conditions may not be the same in all patients [25].

**Insomnia and the comorbid disorder are independent but occur together by chance**
Both insomnia and major depression are very common, so they might often coexist by random chance. This issue has been raised and debated over the years in the context of other sleep disorders, for example the association between depression and narcolepsy [26]. However, in the case of depression and insomnia, this explanation seems unlikely in view of the many studies casting insomnia as a risk factor for depression (e.g. [5,6]), that is, suggesting that the two conditions occur together more commonly than would be found by chance alone.

**Insomnia and the comorbid disorder are both consequences of a more fundamental underlying process**
This view is also consistent with the findings of studies suggesting that insomnia often precedes depression (e.g. [25]). It implies that some underlying process results in both disorders, perhaps with different degrees of sensitivity or different time courses. For example, disturbances of biogenic amine metabolism or receptor function can clearly influence sleep, and may be related to the genesis of depression [27]. Indeed, many therapies for depression, such as the SSRIs, are designed to alter biogenic amine function. This theory has the advantage of parsimony, and it has arisen in other contexts. For instance, there are data suggesting that painful conditions may be one expression of depression [28], and a possible explanation is that biogenic amine function is important in both pain and mood regulation. A related hypothesis (insofar as serotonin is involved in adrenocorticotropic hormone secretion [29]) is that an underlying dysregulation of the hypothalamic–pituitary–adrenal axis might underlie both depression [30] and insomnia [31].

**Insomnia is a consequence of the comorbid condition**
Until recently, this was the traditional view, with the clinical implication that the goal was to treat the “underlying” illness, and that the insomnia would then “take care of itself” [32]. In rationalizing this relationship, an analogy can be made with an inflammatory process designed to protect the body, but which “gets out of hand,” and itself becomes the clinical problem – as in the case of allergic rhinitis. Another analogous example might be pain, which can serve a useful function in warning a person that something is wrong, but which becomes a clinical problem requiring its own treatment when too severe.

One conceptual issue with these analogies is that it is difficult to picture the evolutionary benefit of having disturbed sleep when ill, which later might cause a significant problem. One possibility is that the decreased sleep and increased awakenings might have some vestigial usefulness in increasing the awareness of a dangerous environment. Alternatively, in the case of depression, there are study results indicating that sleep deprivation can be a useful treatment (e.g. [33]); one implication might be that developing sleep disturbance in depression might be an attempt at self-healing.

A larger challenge to the notion that insomnia should be treated as a consequence of the comorbid condition comes from the studies outlined earlier, which, although not fully consistent, suggest that in some situations treating the sleep disturbance may aid in the management of the other disorder (e.g. [7]).

It is important to consider that these alternative approaches are not mutually exclusive. One could speculate that
insomnia and depression are independent processes that can randomly occur together, but then interact with each other as comorbid disorders: mood disturbance might affect sleep, and disturbed sleep in turn might inhibit mood regulation. A conceivable result is a mutually reinforcing cyclic effect, albeit one that can be tackled therapeutically (i.e. by treating the sleep disturbance in depression).

Finally, of course, it is possible that the relationship between insomnia and the comorbid condition varies with different diseases. One recent study suggests that insomnia may be a “state marker” for depression, but a “trait marker” for anxiety disorders [24]. Clearly, it is too early to make definitive judgments about the relationships between insomnia and coexisting conditions, but it seems likely to this author that the kinds of associations described above need to be considered in the design of future studies.

Conclusion
The burden of insomnia is characterized by decrements in quality of life, as well as by increased absenteeism from work, accidents, and general healthcare utilization. In clinical practice, insomnia commonly appears in association with another medical or psychiatric illness, and an additional burden of insomnia is its interaction with these coexisting disorders. A growing body of data suggests that addressing such comorbid insomnia may ameliorate the accompanying condition. Insomnia has been shown to be a risk factor for a number of other disorders; however, as a risk factor, its association with a second disorder could, in principle, take several different forms.

Disclosures
The author has acted as a consultant or served on the speakers’ bureau for Neuroroscience Biosciences, Neurogen, Sanofi-Aventis, Sepracor, and Takeda. He is also a consultant to the non-pharmaceutical companies Abiant and VivoMetrics.

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**SLEEP-DISORDERED BREATHING**

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

Gozal D, Crabtree VM, Sans Capdevila O et al.

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

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

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

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

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


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**A nasal cannula can be used to treat obstructive sleep apnea**

McGinley BM, Patil SP, Kirkness JP et al.

As a potential alternative to continuous positive airway pressure, the authors of this study have developed a treatment for obstructive sleep apnea (OSA) that increases pharyngeal pressure by sending warm, humidified air through an open nasal cannula. The findings of this proof-of-concept study suggest that the method may be useful in treating OSA.

The results of several studies have highlighted the heightened risk of serious medical problems, such as cardiovascular
disease, in sufferers of obstructive sleep apnea (OSA) [1]. Poor quality of life, including excessive daytime sleepiness, is also well documented in the population with OSA. Current treatments for OSA include continuous positive airway pressure (CPAP) and, less commonly, oral appliances and surgical procedures. Findings from research on CPAP use have shown patient compliance to be very low, and alternative treatment methods are needed [2].

This study of patients with OSA generated encouraging results using treatment with nasal insufflations (TNI), in which a nasal cannula delivered air to the subjects at a rate of ≤20 L/min. A humidifier and heater regulated the temperature and humidity (30–33°C and 80%, respectively) of air at the cannula’s nasal outlet.

Overall, 11 participants were recruited from the Johns Hopkins Sleep Disorders Center (Baltimore, MD, USA) with a range of apnea severity as recorded during an overnight polysomnography (PSG) test. Subjects had sleep apnea rated as either “mild” (with an apnea–hypopnea index [AHI] of ≥5 to 15 events/h), “moderate” (AHI of 15–30 events/h), or “severe” (AHI of ≥30 events/h). During a titration study carried out on the first night, TNI was applied to subjects during non-rapid eye movement sleep at 0, 10, or 20 L/min for 5-min intervals. On subsequent nights, the participants were randomized to receive either intervals of TNI at 20 L/min, or no TNI. As indicated by reductions in the number of apnea–hypopnea events in all subjects who received TNI, the results from the current study demonstrated a significant improvement in sleep apnea severity with the treatment, regardless of their initial AHI grouping. Compared with no TNI, active treatment was also associated with a reduction in the mean number of respiratory arousals. The severity of inspiratory flow limitation was also found to be improved when comparing the effects of TNI at 20 L/min with those at 10 L/min. This beneficial effect was associated with reduced supraglottic pressure swings and increased peak inspiratory flow with TNI at 20 L/min.

Although CPAP remains the “gold standard” for treating patients with OSA, these results suggest that TNI should be considered when compliance with CPAP is exceptionally low. Treating patients with TNI is less intrusive than conventional CPAP, which may prove beneficial for adherence rates. The current study results demonstrated an overall improvement in AHI with TNI. Therefore, it would be useful to perform additional studies with increased sample sizes, and to generate data representative of the clinical population.

Expansion sphincter pharyngoplasty: a new technique for the treatment of obstructive sleep apnea


The authors of this study aimed to determine the efficacy of expansion sphincter pharyngoplasty (ESP) in the treatment of obstructive sleep apnea (OSA). Forty-five adults meeting the criteria for this surgical procedure were randomized to receive either ESP or the traditional uvulopalatopharyngoplasty procedure. Although both surgical options revealed statistically significant improvements in the apnea–hypopnea indices of the patients, those who underwent ESP showed a higher success rate with minimal complications.

As obstructive sleep apnea (OSA) is caused by either partial or complete collapse of the upper airway at various levels, the traditional surgical option of uvulopalatopharyngoplasty (UPPP) may not provide the most optimal benefits. Recognizing the role of the lateral pharyngeal walls in contributing to the collapse of the airway, the current authors undertook a study to assess whether expansion sphincter pharyngoplasty (ESP), a new surgical procedure whereby tension is created in these walls, would be more efficacious than UPPP in the treatment of OSA. ESP consists of a tonsillectomy, expansion pharyngoplasty, rotation of the palatopharyngeus muscle, and a partial uvulectomy.

The inclusion criteria for the study included small tonsils, a body mass index (BMI) of <30 kg/m², and significant lateral pharyngeal wall collapse. Consecutive patients meeting these criteria (n=45) were randomized to undergo either UPPP (n=22) or ESP (n=23). The participants' mean age was 42.1 years, the mean BMI was 28.7 kg/m², and the preoperative apnea–hypopnea index (AHI) was 42.3±17.1 events/h. Those undergoing ESP had more severe OSA than those in the UPPP group (AHI 44.2±10.2 events/h vs. 38.1±6.46 events/h). The mean AHI improved to 12.0±6.6 events/h in the ESP group (p<0.005), compared with 19.6±7.9 events/h in the UPPP arm (p<0.05). Surgical success, arbitrarily defined as a 50% reduction in AHI and an AHI of <20 events/h, was observed in 82.6% of those who underwent ESP, compared with 68.1% of those assigned to UPPP (p<0.05). Although no significant complications were noted in either group, those randomized to UPPP demonstrated significant lateral pharyngeal wall collapse.

The results demonstrate greater “success” with the ESP procedure than with UPPP in patients with small tonsils, a BMI of <30 kg/m², and evidence of significant lateral collapse.


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pharyngeal wall collapse. However, in this editor's opinion, as the presence of preoperative pharyngeal wall collapse was a significant factor in the outcomes of the ESP procedure, it would be misleading to compare the two procedures and calculate a “success” rate. Furthermore, the patients in this study had a lower mean BMI than the population typically undergoing these procedures in clinical practice. As BMI can be linked to the amount of pharyngeal soft tissue present, it would be interesting to determine whether UPPP would be more efficacious in patients with more soft tissue. Nevertheless, as the results demonstrate, ESP provides a valid surgical option for those who meet its stringent criteria.

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Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea
Otto ME, Belohlavek M, Romero-Corral A et al.

The authors of this study utilized Doppler echocardiography technology to determine the potential structural and functional cardiac changes exhibited by patients with obstructive sleep apnea (OSA), compared with those without. Those with OSA were found to have an increased left atrial size, and left ventricular diastolic dysfunction compared with the control group.

It is well documented in the literature that cardiovascular disease is one of the many comorbidities associated with obstructive sleep apnea (OSA). To better understand disease progression in seemingly healthy OSA patients, it is important to continue to perform studies that focus on the cardiac functioning of this population. The authors of the current article investigated the impact of changes in cardiac function and structure in a relatively healthy population of individuals with and without OSA.

A total of 23 patients with newly diagnosed OSA, an apnea–hypopnea index (AHI) of ≥15 events/h, a body mass index (BMI) of ≥30 kg/m², and an absence of any other medical conditions, were studied. A control group comprised 18 obese subjects without OSA, as based on an overnight polysomnography recording. Doppler echocardiography was used to record left and right ventricular activities, which included measurements of mitral and tricuspid inflow velocities, superior vena cava inflow, and pulmonary artery flow, and imaging of the septum and lateral wall.

The results revealed the OSA patients to have an increased left atrial volume index and a greater mitral annular late diastolic velocity, compared with the control group. Furthermore, the OSA patients exhibited a decreased mitral annular early diastolic velocity, and a greater proportion of the group exhibited an early-to-late diastolic annular ratio of >1, when compared with control participants. Regarding right ventricular function, the results suggested an attenuation of lateral tricuspid annular early diastolic velocity in those with OSA compared with those without.

Using the data from this study it is difficult to speculate on how OSA affects cardiac activity, but the results do provide an insight on specific impairments in left ventricular function. Findings regarding right ventricular function are limited, and, while deficiencies were found, it is unclear what can be concluded. Therefore, it would be beneficial for future studies to focus on the effects of OSA on right ventricular function.

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Positioner – a method for preventing sleep apnea
Loord H, Hultcrantz E.

In a search for novel treatments for patients with sleep apnea, the current authors investigated the utility of a “positioner” device in reducing apnea events and improving daytime sleepiness. The device may be of benefit for those with positional sleep apnea who experience the majority of apneas in the supine position, as it permits wearers to sleep in the lateral position only.

The most common treatment for obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP) therapy. However, patient compliance is markedly low and the findings of several studies have found CPAP compliance to be strongly correlated with patient training and education (see [1] for a review).

Some patients may benefit from alternative treatments, and the authors of the current study evaluated the use of a “positioner,” a device that is not yet commercially available on the market, for those with positional sleep apnea (PSA). The apparatus has three parts: a vest with straps that are fastened to a board, and a pillow that lies on the board. Wearing this device prevents the patient from lying in the supine position; he or she can lie only in a lateral position.

All 23 patients recruited had PSA with >15 apneas/h, with the majority of events taking place in the supine position, and <5 apneas/h in the lateral position. The participants were otherwise healthy, and a total of
Association of restless legs syndrome in type 2 diabetes: a case control study

Although a secondary form of restless legs syndrome (RLS) has been attributed to various conditions, such as iron deficiency and polyneuropathy, it is still unclear to what extent type 2 diabetes has a role. The authors of this case–control study aimed to assess the relationship that exists between the two conditions by analyzing the characteristics of RLS in diabetic patients and delineating the risk factors for its development. The data reveal that although the presence of polyneuropathy is associated with RLS in those with diabetes, diabetes itself remains an independent risk factor for RLS.

Although restless legs syndrome (RLS) is primarily an idiopathic condition, it exists in a secondary form in approximately one-quarter of clinical cases, including in those with iron deficiency, uremia, pregnancy, polyneuropathy, and rheumatoid arthritis (for example, see [1]). To date, no robust studies have been undertaken to delineate the relationship between type 2 diabetes (T2D) and RLS; however, both conditions exhibit polyneuropathy, and diabetic patients are more prone to RLS than those without diabetes. The current authors aimed to determine the extent of the relationship between T2D and RLS with regard to the prevalence, characteristics, and risk factors of RLS in the diabetic population.

The study included 124 consecutive patients with T2D, and 87 control subjects attending an endocrinology department for the follow-up of conditions other than diabetes. Exclusion criteria included Parkinson’s disease, myelopathy, radiculopathy, and dialysis. The presence of RLS was gauged via a four-question assessment proposed by the International Restless Legs Syndrome Study Group. Those who met RLS criteria were asked to answer additional questions with regard to the severity of the condition, age of onset, localization, and symptomatology. Various laboratory values were obtained, including levels of hemoglobin A1c, folate, vitamin B12, and ferritin. A neurologist who was blinded regarding the RLS diagnosis assessed the patients for neuropathy. Patients with T2D were further subdivided into two groups: those affected by RLS (diabetic RLS+) and those without RLS (diabetic RLS–).

The results revealed that the differences between the diabetic patients and the non-diabetic control subjects were increased body mass indices and triglyceride levels in the former, with 33% of the diabetic individuals exhibiting microvascular complications. In all, 22 T2D patients (17.7%) and five control subjects (5.5%) were diagnosed with RLS (p<0.01). Furthermore, 27% of the diabetic RLS+ patients reported a positive family history of the disorder, compared with 40% of the control group affected by RLS. More women were found in the diabetic RLS+ group than in the RLS– group, while the other variables did not differ significantly between these groups. A multivariate analysis of the other studied parameters confirmed that both diabetic peripheral neuropathy and T2D were independent risk factors for RLS. In addition, RLS appeared to be independent from the iron status of the diabetic patients.

As polyneuropathy appeared to be a critical factor in assessing whether T2D alone could account for the presence of RLS, utilizing only a clinical approach to identify neuropathy may have underestimated the degree present and hence skewed the results.


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Rise of blood pressure with periodic limb movements in sleep and wakefulness
Siddiqui F, Strus J, Ming X et al. 

Several reports indicate that periodic limb movements during sleep (PLMS) are associated with alterations in autonomic function. The authors of the present study examined the effect of PLMS on blood pressure and pulse rate. “Fake PLMS,” where subjects were asked to perform voluntary movements mimicking PLMS, were used as a control condition. It was found that naturally occurring PLMS were associated with significant rises in systolic and diastolic blood pressure, whereas fake PLMS were not.

Several reports have indicated that periodic limb movements during sleep (PLMS) are associated with alterations in autonomic function, including variations in heart rate and transient rises in blood pressure [1]. In this study, Siddiqui et al. examined blood pressure and pulse rate during periodic limb movements in 17 patients with restless legs syndrome (RLS). They compared a number of different types of event, including:

- PLMS associated with arousals.
- PLMS without associated arousals.
- Periodic limb movements occurring during wakefulness.
- “Fake PLMS,” whereby participants were asked to perform voluntary movements in wakefulness that mimicked PLMS.

The authors found that all of the naturally occurring types of periodic limb movements were associated with statistically significant rises in systolic and diastolic blood pressure, while fake PLMS were not. No significant effect on heart rate was noted.

The authors conclude that the observed elevations in blood pressure might have long-term adverse cardiovascular consequences. The nature and associated risks of these brief increases in blood pressure remain poorly understood.

An interesting issue raised by these findings, and not discussed by the authors, is the nature of the relationship between the blood pressure rises and the periodic limb movements. Siddiqui et al. assumed that the movements themselves were the cause of the observed effects on blood pressure. However, the fact that the naturally occurring periodic limb movements (including those occurring during wakefulness) led to rises in blood pressure, while the fake ones did not, would seem to imply that the former are occurring as a result of, or in association with, a burst of autonomic activity. These findings suggest that these bursts of autonomic activity may be a more important “window” into the pathological processes occurring in PLMS than the leg movements themselves.


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EPIDEMIOLOGY

APOE ε4 allele, cognitive dysfunction, and obstructive sleep apnea in children
Gozal D, Capdevila OS, Kheirandish-Gozal L et al. 

The aim of the current study authors was to determine whether the neurocognitive dysfunction that is observed in children with obstructive sleep apnea (OSA) is solely determined by the severity of the condition. Habitually snoring and non-snoring children underwent neurocognitive assessment, polysomnography, and serological testing to determine whether the apolipoprotein E (APOE) ε4 allele has in a role in increased sleep-disordered breathing (SDB) and, more specifically, in any ensuing neurocognitive abnormalities. The results revealed that the APOE ε4 allele does in fact have a statistically significant role in increasing the likelihood of SDB and neurocognitive dysfunction.

The apolipoprotein E (APOE) ε4 allele has recently emerged as a marker signifying an increased likelihood of sleep-disordered breathing [1]. As such, the authors of this study aimed to deduce whether the presence of this allele may also account for the neurocognitive dysfunction observed in children with obstructive sleep apnea (OSA).

In all, 345 non-obese children without any chronic medical conditions or genetic disorders underwent overnight polysomnography, a series of neurobehavioral assessments, and serological tests for the APOE ε4 allele. The subjects were categorized into groups comprising 87 non-snoring control individuals, 146 snorers with OSA, and 112 snorers without OSA. Of the latter group, three had positive serological results for the APOE ε4 allele, and 16 had reduced scores in the battery of neurocognitive tests. In addition, the APOE ε4 allele was also observed in 16 of those with OSA, 12 of whom performed poorly in the neurocognitive tests. Conversely, none of the controls had reduced scores in the neurocognitive assessments, nor did they test positively for the allele. The APOE ε4 allele was

INT J SLEEP WAKEFULNESS Vol 1 No 3 2008
Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression

Benedetti F, Dallaspesia S, Fulgosi MC et al.

The authors of this study examined the effects of a single nucleotide polymorphism in a gene called CLOCK, which is known to play a significant part in circadian rhythm, in patients with bipolar depression. They employed actigraphy to elucidate the effects of the polymorphism on diurnal activity and nocturnal sleep, and found one allelic variant of the gene to be associated with worse sleep symptoms.

Recently, the CLOCK gene has been studied in relation to its role in circadian rhythm [1]. The findings of previous investigations have shown the 3111 T/C single nucleotide polymorphism (SNP) of CLOCK to be linked with sleep disruption in schizophrenics [2]. Using actigraphy, the authors of the current study evaluated the role of this SNP on diurnal activity and nocturnal sleep, and found one allelic variant of the gene to be associated with worse sleep symptoms.

The investigators observed that increased evening activity, delayed sleep onset, and less sleep during the night characterized carriers of the CLOCK 3111 C allele, when compared with T/T homozygotes. Furthermore, the lithium-treated patients exhibited increased evening activity levels in both genotype groups; however, the lithium treatment status had no effect on other comparisons.

The findings of the current study demonstrate strong links between the C allele and the distinct diurnal activity levels and sleep disturbance often observed in mood disorders. It would be interesting to add polysomnographic data to these results to investigate the relationships between allelic variants and specific electroencephalographic changes.

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A nationwide survey of excessive daytime sleepiness in Parkinson’s disease in France


The present authors utilized a national survey consisting of questionnaires, such as the Epworth Sleepiness Scale (ESS), to determine the prevalence of excessive daytime sleepiness (EDS) and sudden onset of sleep episodes in patients with Parkinson’s disease. Of the 1625 patients surveyed, 29% revealed symptoms of EDS (ESS score of ≥10), with 0.8% reporting a high chance of dozing when driving. Male gender, reduced activities of daily living, and high doses of levodopa treatment were indicative of EDS.

Although it is recognized that patients with Parkinson’s disease (PD) experience excessive daytime sleepiness (EDS), the extent and cause of this symptom remain unclear. Rather than elucidating an etiology for EDS in their patient population the present authors attempted to determine the frequency and factors involved.

Responses to questionnaires measuring sleepiness (the Epworth Sleepiness Scale (ESS)), Parkinsonian staging, mental functioning, and global disability regarding activities of daily living were included in the analysis. Participants (699 women and 923 men, mean age 69.5±9.3 years) rated their likelihood of “dozing” and experiencing “sudden onset of sleep episodes” (SOS) when driving. In addition, patients’ medications and respective doses were recorded.
The questionnaires results revealed a 29% prevalence of EDS (ESS score of ≥10), with 65% of the affected individuals being male. Independent predictive factors for EDS included:

- Male gender.
- Disability regarding activities of daily living.
- Levodopa dosage.

The use of dopamine agonists, either alone or in combination with levodopa, did not significantly alter the ESS scores. A high chance of dozing while driving was reported by 0.8% of the participants, while 0.5% reported erratic episodes of SOS.

Although this study illustrates the prevalence and degree of sleepiness in a large cohort of patients with PD, due to a lack of objective findings the results fail to bolster the authors’ conclusions. Certainly, use of polysomnography or the Multiple Sleep Latency Test would have been useful in excluding disorders such as sleep-disordered breathing, idiopathic hypersonolence, or periodic limb movements in sleep, which are known to impact upon EDS. Furthermore, as the participants were ambulatory a large portion of the population with PD was excluded. This makes generalization of the results across the entire group problematic.

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**INSOMNIA**

Insomnia in places of detention: a review of the most recent research findings

Elger BS.


Elger carried out this literature review in order to determine the prevalence, characteristics, and treatment of insomnia in places of detention. The review identified that little systematic research on the management of insomnia in this setting has been carried out, and therefore it is not possible to draw firm conclusions. The author cites some evidence that insomnia frequently occurs independently of psychiatric or medical disorders, and speculates that this is partly due to “situational” factors related to incarceration.

Insomnia is known to be more prevalent in individuals in places of detention than in members of the general population. However, little is known of the occurrence of the condition and its management in this setting. In the current article, Elger reviewed the available literature in order to determine the prevalence, characteristics, and treatment of insomnia in places of detention. Specifically, the intention was to explore whether insomnia:

- Occurred in association with any pre-existing psychiatric disorder, such as post-traumatic stress disorder, or substance abuse.
- Was a response to incarceration-related factors, such as noise, light, promiscuity, violence, and rape.
- Was due to new anxiety and depression symptoms arising as a result of incarceration.

The author identifies the fact that little systematic data exist regarding insomnia occurring in places of detention. What limited evidence is available in the literature suggests that, globally, a variety of approaches are taken for diagnosis and treatment, with no emergence of a clear pattern. Lacking the findings from controlled trials, the author claims that it is impossible to draw any conclusions regarding the effectiveness of these different approaches.

There is some evidence that, while insomnia does occur in places of detention in association with psychiatric disorders, it also frequently arises independently of psychiatric or medical conditions [1]. The author speculates that this independent insomnia is, at least in part, due to “situational” factors related to incarceration; that is, the condition occurs because of ongoing stressors or environmental factors.

At the same time, the present article brings attention to the issue of treating chronic “situational” insomnia. This is an issue that also applies to individuals who are not in places of detention. These people are likely to have treatment needs that differ from those of individuals with classically defined insomnia, who have an undisturbed opportunity to sleep but are unable to do so. Many short-term, placebo-controlled studies regarding the effects of insomnia treatments on sleep disruption due to sound, or other sleep-disturbing factors, have been carried out and have revealed significant therapeutic effects compared with placebo (e.g. [2]). How the response to treatment for such individuals differs from that in people with chronic “situational” insomnia remains to be determined.

NARCOLEPSY

REM sleep characteristics in narcolepsy and REM sleep behavior disorder

Although both narcolepsy and rapid eye movement (REM) behavior disorder (RBD) are characterized by REM sleep dysfunction, it remains unclear which polysomnographic characteristics, if any, distinguish the two. The aim of the present authors was to assess the polysomnographic abnormalities in a small cohort of narcoleptic subjects compared with those of control participants and RBD patients.

Abnormalities in rapid eye movement (REM) sleep are characteristic both of narcolepsy and of REM behavior disorder (RBD). Thus, one might surmise that both conditions can be correlated objectively using polysomnography (PSG). The authors of the present study attempted to investigate whether narcoleptic signifiers can indeed be verified and their values compared with those of control subjects and RBD patients.

Sixteen patients who met the criteria for narcolepsy with cataplexy, and 16 with “idiopathic” RBD (that is, excluding conditions known to be associated with RBD, such as Parkinson disease, multiple system atrophy, and dementia with Lewy bodies), were age- and sex-matched to 16 healthy control subjects. All participants underwent PSG and the narcoleptic patients had a Multiple Sleep Latency Test following the nocturnal sleep study. Measured parameters included the two types of phasic activity of REM sleep, REM density, and periodic limb movements while awake (PLMW) and while asleep (PLMS). None of the patients exhibited an apnea–hypopnea index >5 events/h or a respiratory distress index >10 events/h.

Although patients with narcolepsy and those with RBD had greater PLMW and PLMS indices compared with the control group, only the former showed a statistically significant difference. Both the RBD and narcoleptic patients had a lower percentage of REM sleep atonia than the control subjects, with the former group showing a more robust difference. Furthermore, patients with RBD had a significantly greater phasic motor activity in REM sleep. However, narcolepsy patients showed higher REM density than both the control group and the patients with RBD.

These findings thus implicate a tenuous but significant relationship between narcolepsy and RBD with regard to the observed REM sleep characteristics. However, since video recording was not available during the sleep studies, the extent of the motor manifestations that could have been missed in those with narcolepsy is uncertain.

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Amygdala dysfunction in narcolepsy-cataplexy

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

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

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

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

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CSF hypocretin-1 levels and clinical profiles in narcolepsy and idiopathic CNS hypersomnia in Norway


The authors of this study utilized the cerebrospinal fluid hypocretin (orexin)-1 levels of patients diagnosed with narcolepsy, with and without cataplexy, and those with idiopathic hypersomnia to determine whether these values signify certain differentiating profiles. Data regarding human leukocyte antigen serology were also collected. The results revealed that although narcolepsy with cataplexy was significantly associated with low hypocretin levels in this subset of patients, no robust differences were observed between patients with narcolepsy without cataplexy and those with idiopathic central nervous system (CNS) hypersomnia.

Although the diagnosis of narcolepsy rests on various symptomatologies and objective data, the measurement of cerebrospinal fluid (CSF) hypocretin (orexin)-1 levels has come to represent a distinct tool for the identification of narcolepsy with cataplexy. In addition, the serological presence of the human leukocyte antigen (HLA)-type DQB1*0602 in those with narcolepsy has been utilized for this function. However, since 25% of the general European population also harbors this HLA, its role as a diagnostic aid has limited utility. The current authors broached further issues related to the hypocretins by assessing whether these neuropeptides are suggestive of specific characteristics in patients with narcolepsy, both with and without cataplexy, and those with idiopathic CNS hypersomnia.

In all, 64 patients who were diagnosed with one of these disorders by meeting the specific inclusion criteria were enrolled in the study, and had their CSF or blood collected for a determination of hypocretin-1 levels or HLA-DQB1*0602, respectively. HLA-DQB1*0602 positivity was identified in 43 of 47 people with narcolepsy with cataplexy, two of seven with narcolepsy without cataplexy, and four of 10 with idiopathic CNS hypersomnia. Of the patients with narcolepsy with cataplexy and HLA positivity, 31 had significantly reduced hypocretin-1 values (mean 85.9 pg/mL). The remaining 12 had values within the normal range, which did not differ significantly from the hypocretin-1 levels of both patients with narcolepsy without cataplexy and those with idiopathic CNS hypersomnia.

With regard to clinical symptomatologies, 90% of the narcoleptic patients with cataplexy and low hypocretin-1 levels experienced cataplectic attacks that involved mainly the jaw, face, and neck muscles, whereas just 56% of patients with normal levels of hypocretin-1 reported this (p=0.020). No significant differences were found in the frequency of hypnagogic hallucinations and sleep paralysis between patients with cataplexy who harbored low and normal CSF hypocretin-1 values. Although the patients with CNS hypersomnia or narcolepsy without cataplexy reported a lower frequency of sleep paralysis than the entire cohort of patients with cataplexy, no significant differences were observed between the various groups with regard to the frequency of hypnagogic hallucinations. In addition, no correlation was observed between the duration of the narcolepsy and the CSF levels of hypocretin-1 in any of the groups.

The authors conclude that there is a distinct subgroup of narcoleptic patients who present with HLA-DQB1*0602 positivity, cataplexy, and low CSF hypocretin-1 values. Interestingly, there were no significant clinical or objective differences between narcoleptics without cataplexy and those with idiopathic CNS hypersomnia, with the exception of the two or more sleep-onset rapid eye movement periods that define the former. As the authors of this study strictly delineated the clinical criterion of cataplexy, including only “classically” mediated forms, it is possible that some of the narcoleptics were “miscategorized,” thus altering the clinical symptoms and objective data.

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Reduced expression of TACI, PENK and SOCS2 in Hcrtr-2 mutated narcoleptic dog brain


The findings of the current study demonstrate that the expression of two neuropeptide precursor molecules and the protein suppressor of cytokine signaling 2 is reduced in the brains of narcoleptic dogs, compared with their healthy siblings. This effect was most pronounced in the amygdala and pons.

Narcolepsy is a debilitating neurological disease characterized by abnormally fragmented sleep – specifically, shortened sleep latency accompanied by daytime sleepiness, and cataplectic episodes that typically occur in response to emotional stimuli. The authors of this article examined two neuropeptide precursor molecules, tachykinin precursor 1 and proenkephalin, along with the protein suppressor of cytokine signaling 2 (expressed by the genes TAC1, PENK, and SOCS2, respectively) in the narcoleptic dog brain.

The authors had a rare opportunity to study six narcoleptic Doberman dogs (homozygous for a mutation in...
the hypocretin receptor 2 gene, HCRTR2) and their healthy heterozygous siblings, with both groups raised in the same environmental conditions. The expression patterns of 29,760 genes were compared in the hypothalamus, amygdala, and pons using microarrays. As confirmed using real-time reverse transcriptase polymerase chain reaction studies, PENK, SOCS2, and TAC1, were found to have a downregulated expression profile in the narcoleptic dogs compared with their healthy counterparts, with this effect being most notable in the amygdala and pons.

Narcolepsy is a debilitating disorder and its foundations are being slowly uncovered. The findings of this study provide greater insights into the genes and specific areas of the brain that require further investigation in humans.

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**CLINICAL MANAGEMENT**

A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia

Pierre JM, Peloian JH, Wirshing DA et al.


The deficit symptoms of schizophrenia, such as flattening of affect, cognitive impairment, lack of motivation, social withdrawal, and disorganized behavior, can have a great impact on the lives of affected individuals. The authors of this article performed a double-blind, placebo-controlled study to determine whether augmenting stable antipsychotic therapy with the wake-promoting agent modafinil has a therapeutic effect on these symptoms. Modafinil treatment led to significant improvements compared with placebo on clinical global improvement ratings, but no effect was found on any measures of deficit symptoms. The global improvement noted might indicate a therapeutic effect on the daytime sedation that often accompanies treatment with antipsychotic agents.

Psychotic symptoms consisting of hallucinations and delusions are the best-known features of schizophrenia. However, the deficit symptoms of the condition, such as flattening of affect, cognitive impairment, lack of motivation, social withdrawal, and disorganized behavior, can have a significant impact on the lives of affected individuals.

One strategy for addressing these symptoms is to augment antipsychotic therapy with a treatment that targets a specific deficit. Although not currently licensed for treating deficit symptoms of schizophrenia, based on the evidence from a case report [1], and one open-label study [2], the present authors carried out the first double-blind, placebo-controlled investigation of augmentation therapy with modafinil.

The study involved 20 patients with schizophrenia, who were maintained on stable antipsychotic medication and were treated with either placebo or adjunctive modafinil for 8 weeks. While treatment with modafinil led to a significant improvement in ratings on the Clinical Global Impression – Improvement Scale compared with placebo, no significant effect was found on any measures of deficit symptoms. Interestingly, contrary to previous reports [3], there was no evidence that modafinil worsened the psychotic symptoms in these patients.

In summary, the results from the current study suggest that modafinil does not have a therapeutic effect on deficit symptoms in schizophrenia patients. The nature of the global improvements recorded is unclear. One possibility for consideration is that modafinil may have had a therapeutic effect on the daytime sedation that often accompanies treatment with antipsychotic agents.


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A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression

Frye MA, Gronze H, Suppes T et al.


The authors of this multicenter study aimed to determine whether or not adjunctive modafinil is an effective and safe therapy for bipolar depression. Positive outcomes were observed for several measures, and included improvements in depressive symptoms and energy.

Due to the small number of pharmaceutical medications available for bipolar depression, it is important to continue clinical research on potential therapies in order to expand the range of available options for patients. In the current study, the investigators evaluated the safety and efficacy of modafinil as such a treatment. Modafinil is a commonly prescribed wake-promoting agent, which is utilized in the treatment of various sleep disorders. It has also been shown in clinical studies to improve attention deficit hyperactivity disorder, cocaine dependence, and unipolar depression; however, it is not currently licensed for these indications.
Snoring is considered to be not only a social nuisance but also a potential signifier of sleep-disordered breathing. Various surgical techniques have been utilized to create scar tissue, ultimately leading to palatal stiffening that could ameliorate the condition. The authors of the present study aimed to assess whether a modified form of a palatal stiffening operation, first devised in 1994 [1], could provide objective and subjective success in treating those with snoring and mild obstructive sleep apnea (OSA).

Thirteen patients who met the inclusion criteria (including age of >18 years, a body mass index [BMI] of <33 kg/m², tonsil size of grades 1 or 2, an elongated uvula, and an apnea–hypopnea index of <15 events/h) were enrolled in the study and underwent the modified cautery-assisted palatal stiffening operation (CAPSO). A comprehensive clinical assessment was performed on each patient and included a physical examination, nasendoscopy, and an overnight, attended polysomnography (PSG) recording. The patients also completed various subjective assessments, such as the Epworth Sleepiness Scale (ESS) and a visual analogue scale (VAS) for both pain and snoring, pre- and post-operatively. The procedure itself was performed in an outpatient setting under local anesthesia and participants were administered various analgesics to be used symptomatically.

Of the 13 patients who underwent the modified CAPSO, five were simple snorers (mean AHI of 3.9 events/h) and eight showed evidence of mild OSA (mean AHI of 12.3 events/h). The participants were all men, with a mean age of 35.7 years and a mean BMI of 28.4 kg/m². A PSG recording performed 3 months postoperatively revealed improvements both in mean AHI, from 12.3 to 5.2 events/h (p<0.05), and in the lowest oxygen saturation, from 88.3% to 92.5% (p<0.05). All subjects reported improvements in snoring and ESS score, and pain appeared to be the most significant complaint, showing amelioration over a span of 14 days. Interestingly, no beneficial effects were noted regarding sleep architecture, in terms of the proportions of slow-wave or rapid eye movement sleep.

The authors conclude that the modified CAPSO is a promising and effective surgical option for patients who meet its criteria. The procedure is brief, inexpensive, and can be accomplished in an outpatient setting, presenting an alternative to laser-assisted uvulopalatoplasty. A shortcoming of the study is the small size of the sample, which may not provide an accurate representation of even those who meet its strict criteria.

Fixed and autoadjusting continuous positive airway pressure treatments are not similar in reducing cardiovascular risk factors in patients with obstructive sleep apnea

Auto-adjusting continuous positive airway pressure (ACPAP) treatment is an attractive alternative to standard, fixed-pressure CPAP therapy for obstructive sleep apnea (OSA). This is because of the possibility that ACPAP achieves better pressure optimization, and potentially obviates the need to perform the costly pressure-titration procedure required to implement CPAP. The investigators of the current study compared the effectiveness of these two forms of therapy in a 3-month, randomized trial. While ACPAP and CPAP had similar therapeutic effects on OSA severity indices, CPAP led to significantly lower apnea–hypopnea and oxyhemoglobin desaturation indices. These effects were accompanied by greater improvements in systolic and diastolic blood pressure and a measure of insulin resistance with CPAP.

The authors report that ACPAP and CPAP achieved similar therapeutic effects on the measures of OSA severity and CRP level; however, CPAP led to significant improvements in systolic and diastolic blood pressure and HOMA-IR, whereas ACPAP did not. The authors conclude that CPAP may provide superior benefit in terms of addressing the cardiovascular risks of OSA.

In considering the findings of this study, it is important to bear in mind that these results apply only to the specific type of ACPAP employed in this study, and therefore may reflect the limitations of the algorithm of that device. Another important consideration is that there were significant differences between the effects of the ACPAP and CPAP on some of the key OSA severity indices. Most notably, CPAP treatment led to a significantly lower AHI than did ACPAP (2 events/h vs. 6 events/h; p<0.001), and was also associated with a reduced oxyhemoglobin desaturation index (1.1 events/h vs. 4.8 events/h; p<0.001).

Without such knowledge, it would be hard to explain how CPAP treatment might have had a greater effect on cardiovascular risk factors than therapy with ACPAP, and may have led one to hypothesize that the treatment pressures needed to eliminate the risks for some of the sequelae of OSA are different from those needed to eradicate OSA events themselves, as traditionally defined. Instead, this study provides preliminary evidence that even apparently small differences in OSA severity may have substantive effects on some of the risk factors for related sequelae. In conclusion, the findings suggest the need to achieve a high level of remission with therapy, perhaps beyond that which can be obtained with at least some of the current ACPAP devices.

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

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

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

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

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

Dr Czeisler presented a highly informative and personal view of the impact of sleep loss on driving and physician performance (see [3–7] for related publications), describing the frustrations faced in attempts at changing public attitudes and shift-work patterns. He pleaded with sleep physicians to take leading roles in changing outdated policies (especially regarding those for trainee physicians) that, in his view, put lives at risk. He additionally highlighted the current challenges faced by sleep medicine professionals, such as reducing waiting times for the diagnosis of sleep-disordered breathing (SDB), implementing clinical standards
for diagnosis, developing innovative techniques to treat obstructive sleep apnea (OSA), and improving patient adherence to existing treatments. The overriding sentiment was that healthcare professionals must not be complacent regarding the hazards of sleep deprivation.

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

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

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

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

**Meeting themes**

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

**Sleep in children**

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

Raouf Amin (Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA) reported that children with SDB have greater blood-pressure variability in response to respiratory events compared with those without the condition. However, in a study in which children with SDB were matched with control subjects, and those with comorbidities were excluded, he observed that children with SDB did not exhibit a greater prevalence of pulmonary hypertension than their control counterparts.
David Gozal (University of Louisville, Louisville, KY, USA) outlined his previous and recent studies examining OSA in childhood. He suggested that hypoxia secondary to OSA is associated with inflammatory changes that predispose children to develop cardiovascular disease, independently of body weight. In a discussion on inflammatory markers of OSA, he proposed a triple-risk, OSA morbidity model, which implies an interaction between the environment, OSA severity, and individual susceptibility to cardiovascular disease. He said that when taken together, these findings argue for the inclusion of measurements of subcortical arousal, continuous blood pressure, and heart-rate variability in PSG montages for children with suspected SDB.

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

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

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

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

Interest in the function of slow-wave sleep (SWS) and slow-wave activity (SWA) has stimulated research in a number of different areas. Derk-Jan Dijk (University of Surrey, Guildford, UK) suggested that, based on evidence regarding the neurocognitive effects of SWS deprivation, slow waves may be regulated homeostatically. In his study, disruption of SWS resulted in both subjective and objective daytime sleepiness effects, with significant increases in...
scores recorded on the Karolinska Sleepiness Scale and in sleep propensity, as measured using the MSLT. In addition, SWS deprivation caused errors of commission, attention-modulated motion sensitivity, and motor tracking, but it had no effect on working memory. Interestingly, it was found that for performance tests in which the results did not respond to SWS disruption, there was a response to TSD, suggesting a homeostatic mechanism.

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

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

The hypocretin system and pharmacotherapy: new developments

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

Disclosures

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

References

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