

# *The International Journal of* **SLEEP DISORDERS**

*Applying the evidence in sleep medicine*

**EDITOR-IN-CHIEF**

Alan F Schatzberg, Stanford, CA, USA

**LEADING ARTICLES**

**Restless Legs Syndrome:  
A Review of Diagnosis and Management**

*Sharon Muzerengi, Helen Lewis, and K-Ray Chaudhuri*

**Sleep-Disordered Breathing in Children**

*Rafael Pelayo*



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## Aims and Scope

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

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

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

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

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Dear Colleagues,

Welcome to the second issue of *The International Journal of Sleep Disorders*.

In our first leading article, Drs Muzerengi, Lewis, and Chaudhuri review restless legs syndrome (RLS), describing its epidemiology, possible etiologies, and the available treatments for this disorder. The dopaminergic and opiate- and iron-linked pathways of the central nervous system have been implicated in the pathogenesis of RLS, and a possible genetic basis for this disorder has also been suggested; however, the true cause remains elusive. The dopamine agonists ropinirole and pramipexole have recently been licensed for treatment of RLS (pramipexole is not yet licensed in the US). This will hopefully improve the quality of life of these patients and highlights the growing importance accredited to the research and understanding of sleep disorders.

Our second article again focuses on the importance of sufficient and satisfactory sleep, this time reviewing sleep-disordered breathing (SDB) in children. Children with SDB have a higher prevalence of behavioral problems such as hyperactivity and emotional lability, and an association has been noted between SDB and attention deficit-hyperactivity disorder. Symptoms of SDB can also include excessive daytime sleepiness, bedwetting, parasomnias, and restless or non-refreshing sleep. Adenotonsillectomy is commonly recommended as a treatment for children with SDB; however, it is important to establish that no symptoms of SDB remain after this operation as unidentified residual SDB may further contribute to behavioural problems and learning difficulties.

These articles are followed by a synopsis of the latest and most important scientific findings, reviewed and placed into clinical context to provide a digested read of the most critical developments from several key areas of sleep research.

The issue concludes with highlights from two of the most important meetings in the world of sleep medicine: the American Psychiatric Association's 159th Annual Meeting and the 20th anniversary meeting of the Associated Professional Sleep Societies.

We would like to thank you for the positive response to the first issue of *The International Journal of Sleep Disorders* and look forward to receiving your comments and suggestions in the future to help us to continue to provide a useful resource for clinicians working in this rapidly developing field.

Alan F Schatzberg  
Editor-in-Chief

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# Restless Legs Syndrome: A Review of Diagnosis and Management

Sharon Muzerengi<sup>1</sup>, Helen Lewis<sup>2</sup>, and K Ray Chaudhuri<sup>1,2</sup>

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**Restless legs syndrome (RLS) is a chronic sensorimotor disorder; however, despite its reported high prevalence and adverse effects on quality of life, the condition has remained under-recognized, under-treated, and sometimes trivialized by the media. Factors, including the dopaminergic and opiate- and iron-linked pathways of the central nervous system, and a genetic basis have been implicated in the pathogenesis of RLS, but the actual cause remains unclear. Several classes of drugs have been evaluated for the treatment of RLS, with dopamine agonists now recommended as first-line therapy for RLS in most of Europe and USA. This review aims to address the pathophysiology of RLS, and its presentation, diagnosis, and management. *Int J Sleep Disorders* 2006;1(2):42–54.**

Restless legs syndrome (RLS) is a common movement disorder with sensorimotor symptoms that occurs during sleep and quiet wakefulness. It is considered by some to be the most common movement disorder affecting sleep and daytime functioning. RLS is characterized by a strong urge to move the legs, usually accompanied by paraesthesia or dysesthesia in the affected limbs, and occurs in a circadian pattern. The term RLS was first introduced in 1945 by a Swedish neurologist and surgeon Karl-Axel Ekbom, who described and systematically characterized the condition; as such, it is also known as Ekbom's syndrome [1].

RLS is common and widely accepted to affect 7–9% of the Caucasian population, frequently presenting in both primary and secondary care. However, the condition remains under-recognized, and is often misrepresented and misdiagnosed as a psychogenic disorder. Indeed, in 1994, Yoakum perhaps appropriately described RLS as “the most common disorder you've never heard of” [2].

In the past couple of decades our understanding of RLS has dramatically increased. A number of studies have shown that RLS adversely affects quality of life when undiagnosed or inappropriately treated [3–7], and can impair cognitive ability [8]. There is a growing evidence base for effective lifestyle and pharmacological management strategies for RLS and recently, two dopamine agonists have become the first licensed agents for specific treatment of RLS in the UK and most of Europe. In this review, we aim to highlight the

pathophysiology, diagnosis, and treatment of RLS, so that management of this condition can be attempted in a “holistic” fashion.

## The history of RLS

RLS was possibly described in the 17th century, although it is claimed that ancient Chinese literature describes conditions similar to RLS. In 1672, the English physician Sir Thomas Willis described sleep problems associated with RLS in a chapter entitled “Instructions for Curing the Watching Evil” in Latin [9].

“Wherefore to some, when being abed they betake themselves to sleep, presently in the arms and legs, leapings and contractions to the tendons, and so great a restlessness and tossing of their members ensue, that the diseased are no more able to sleep than if they were in a place of greatest torture.”

In the 19th century, Wittmaak the used term “anxietas tibiarius” to describe a syndrome similar to RLS [10], and in France the term “impatience musculaire” was used. In his original description of the condition in 1945, Ekbom distinguished between the sensory form of RLS (asthenia crurum paraesthesia) and the painful variant of RLS (asthenia crurum dolorosa) [1]. More recently, abnormal involuntary movements during sleep such as nocturnal myoclonus (subsequently termed periodic limb movements during sleep [PLMS]) have been reported to have a strong association with RLS [11,12]. In 1995, the International RLS Study Group (IRLSSG) published a set of validated diagnostic criteria allowing for easier and standardized diagnosis of the syndrome [13]. Revised criteria for RLS

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**Table 1.** Associated and supportive features of RLS.

Supportive features	Associated features
Response to dopaminergic drugs	Clinical course (usually progressive but non-progressive or remitting course may be seen)
PLMS or PLMW	Neurological examination (normal in idiopathic RLS)
Family history of RLS (family history is seen in approximately 50–92% of idiopathic RLS patients)	Sleep disturbance (usually insomnia)

PLMS: periodic limb movement – sleep state; PLMW: periodic limb movement – wake state; RLS: restless legs syndrome.

diagnosis were formulated from a consensus conference held at the National Institutes of Health during May 2002 in Bethesda, MA, USA [14].

Through a serendipitous finding, Akpinar discovered that even a relatively small dose of levodopa can provide dramatic relief of very severe RLS symptoms [15]. However, the adverse effects of levodopa therapy for RLS, augmentation and rebound, were first described by Allen and Earley in 1996 and led to the widespread use of dopamine agonists rather than levodopa for treatment of RLS [16].

## Epidemiology

Most epidemiological studies before 1995 were limited by confounding variables due to the absence of any unifying standard diagnostic criteria. Recent studies have been more thorough, and using IRLSSG criteria have revealed that RLS is a common neurological disorder with prevalence rates of 2.5–10% among various regions of the world [17–19]. Prevalence rates as high as 15% have also been reported [20], although studies in Singapore Chinese (0.1%), Japanese (1.06%), and Indian (0.8%) populations suggest a low prevalence in these ethnic groups [21–23]. At the present time there are no prevalence studies available for the black population [24].

RLS is poorly recognized in primary care. Results from the INSTANT study in France showed that of the 53% of individuals who consulted a primary care physician about their symptoms, only 5.3% received the correct diagnosis [19]. The REST (RLS Epidemiology, Symptoms, and Treatment) primary care study reported that the majority of patients with RLS present to their doctor, but only 12.9% are accurately diagnosed [25]. Although RLS is more common among the elderly, symptoms can start at any age, including during childhood [26,27]. Most studies reveal a higher prevalence among females [17,28], and recent evidence suggest that parity may explain the gender difference as RLS is common during pregnancy [28].

## Clinical features

The classical clinical diagnostic features of RLS, as defined by the IRLSSG criteria, are [14]:

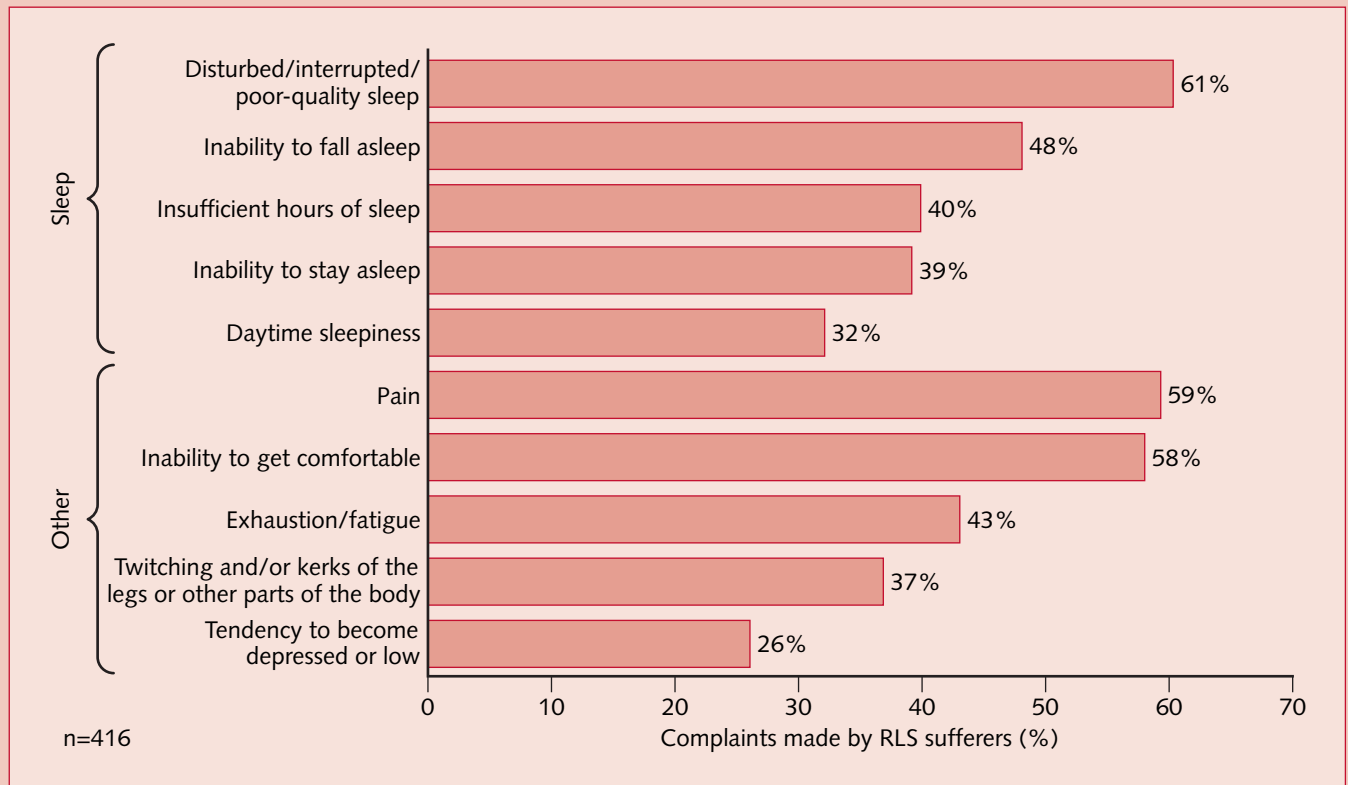
- Criterion 1: An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations (sometimes the urge to move is present without the uncomfortable sensations. The arms or other body parts can be involved in addition to the legs).
- Criterion 2: The urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity, such as lying or sitting.
- Criterion 3: The urge to move or unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, for at least as long as the activity continues.
- Criterion 4: The urge to move or unpleasant sensations that are worse in the evening or night than during the day, or only occur during the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

There are also several additional “supportive” or “associated” features, as shown in Table 1.

The REST study noted the troublesome clinical symptoms of RLS, with the most consistent presenting problem for RLS patients being disturbed or poor sleep quality and sleep-onset insomnia (Fig. 1) [25]. The authors' own observation from the National RLS clinic in London, UK also supports this observation (Fig. 2) [29]. Upper limb involvement is not unusual, and in one study 48.7% of patients with severe primary RLS had arm restlessness [30]. Although the symptoms are usually bilateral, one limb may be more affected than the other. A wide variety of descriptions have been documented for the sensations that often accompany the urge to move the limbs, and are outlined in Table 2.

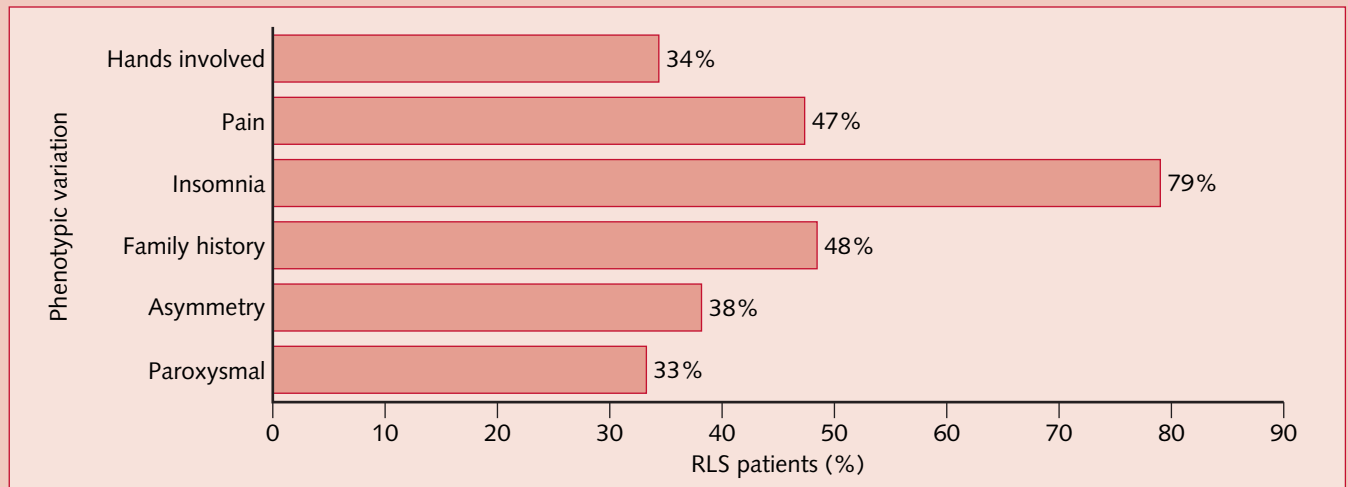
Symptoms of primary or idiopathic RLS can appear at any age, and Allen and Earley suggested that two common phenotypes can be clinically recognized according to age of onset; these are classed as early- and late- onset RLS. Early-onset RLS (onset of symptoms before the age of 45 years) is characterized by slow progressive symptoms

**Figure 1.** Most troublesome symptoms of RLS in primary care patients in the REST study [25].



REST: RLS Epidemiology, Symptoms, and Treatment; RLS: restless legs syndrome.

**Figure 2.** Phenotypic variation in symptoms of patients with RLS [29].



RLS: restless legs syndrome.

over several years and has a strong genetic basis [31]. The first-degree relatives of patients with early onset RLS have been reported to be at a five-fold higher risk for RLS than the general population. Late-onset RLS is usually non-progressive and sporadic, and is often linked to low ferritin levels.

### Pathophysiology

The underlying pathophysiology of RLS is largely unknown. However, contributory factors have been proposed that include central and peripheral nervous system involvement with vascular, genetic, iatrogenic, and metabolic components [6,24]. There is some evidence from pharmacological and

**Table 2.** Patient descriptions of restless legs syndrome sensations in the legs.

Aching in my bones
Like coca-cola bubbling through my veins
Crazy legs
Creepy-crawly
Elvis legs
The gotta-moves
Growing pains
The heeby-jeebies
Itching bones
Like maggots crawling through my veins
Like a tooth-ache in the legs
Pulling
Pain
Tearing
Throbbing

imaging studies for the involvement of the central dopamine pathways, in particular the striatonigral system, while others have suggested that abnormalities in the central nervous system (CNS) iron regulatory pathways have a key role in the development of RLS [32,33]. Iron is interlinked with dopamine pathways in the brain and also exhibits a strong circadian rhythm, similar to dopamine.

### Genetic factors

There is a strong hereditary aspect to RLS and familial aggregation of RLS is common. Molecular genetics studies have shown that there are susceptibility loci on chromosomes 12q, 14q, and 9p, termed RLS-1, RLS-2 and RLS-3, respectively [34,35]. However, this heritability may not apply to all types of RLS. Ondo and Jankovic reported a large difference in the percentage of patients with a positive family history of RLS when they compared patients with idiopathic and neuropathic RLS (RLS associated with peripheral neuropathy) [36]. Of the patients with idiopathic RLS, 92% had a positive family history compared with only 13% of those with neuropathic RLS; a difference in the age of onset was also noted.

Several investigations of single families have suggested that there may be an autosomal dominant form of inheritance with variable expression, and possible genetic anticipation has been shown in some families [37,38]. In support of this, Scholls and colleagues verified that RLS is prevalent amongst patients with spinocerebellar ataxia type 3 (SCA3), but less common amongst other forms of

**Table 3.** Candidate genes investigated in restless legs syndrome; none of which have had linkage identified [35].

Candidate gene
Dopamine receptor genes:
D <sub>1</sub> -D <sub>5</sub> receptors
DAT (dopamine transporter)
TH (Tyrosine hydroxylase)
Dopamine β-hydroxylase
GTP-cyclohydrolase
GABA <sub>A</sub> receptor subunits (α1-6, β1-3, χ1-3, p1-2)
α1 subunit of the glycine receptor (chromosome 5, q31)
MAO A
MAO
Neurotensin

GABA: γ-aminobutyric acid; GTP: guanosine triphosphate;  
MAO: monoamine oxidase.

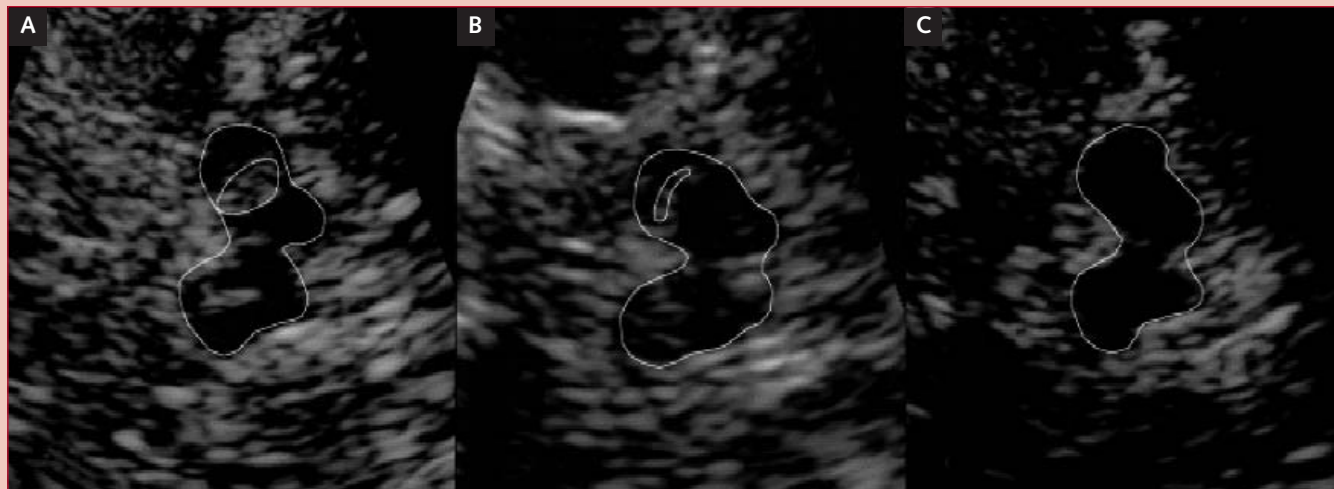
autosomal dominant cerebellar ataxias. This suggests that the expanding CAG repeat in the SCA3 gene may represent a molecular cause of RLS [39], although this remains unproven [40]. There have been various studies of candidate genes for the development of RLS, with particular emphasis placed on those involved in central dopaminergic transmission (Table 3). In 96 unrelated patients, Desautels et al. found that females with high activity alleles of the monoamine oxidase-A polymorphism were at a two-fold greater risk of developing RLS than females with low activity alleles [41]. No such correlation was found in male subjects. Other studies into candidate genes in the susceptibility loci identified have as yet failed to yield positive results.

### Dopaminergic involvement

Evidence suggests that dysfunction of the dopaminergic system of the brain and possibly the spinal cord may contribute to the pathogenesis of RLS [42]. The occurrence of RLS symptoms at night coincides with low levels of dopamine, and these symptoms respond to dopaminergic drugs, in particular D<sub>2</sub> active dopamine agonists.

Some functional brain imaging studies (using positron emission tomography [PET] and photon emission computer tomography [SPECT]) have also shown a slight but significant decrease in striatal dopamine binding and uptake [43-46]. However, other studies have reported no differences in presynaptic (dopamine transporter) or post-synaptic (<sup>123</sup>I-IBZM) D<sub>2</sub> receptor binding [47]. Linke and colleagues used SPECT and <sup>123</sup>I-IPT (a tropane ligand) to investigate the striatal dopamine transporter in 28 patients

**Figure 3.** Transcranial ultrasound appearances (axial scanning plane) in three patients. **A.** Patient with Parkinson's disease. **B.** Control subject. **C.** Patient with restless legs syndrome. Midbrain and areas of hyperechogenicity encircled in (A) and (B) and hypoechogenicity in (C) on the side of insonation.



Reproduced with permission from [59].

with RLS, 29 with early Parkinson's disease (PD), and 23 age-matched controls [48]. They reported no difference in  $^{123}\text{I}$ -IPT binding between RLS patients and controls; PD patients had low uptake on SPECT as expected. This study therefore disputes a link between RLS and PD based on nigrostriatal presynaptic dopaminergic dysfunction. A recent study by Mrowka and colleagues investigated RLS patients and controls using a three-dimensional ultrasound-based movement analysis before and after a levodopa test dose, and beta CIT-SPECT scans [49]. No significant change in movement analysis response to levodopa or differences in beta-CIT signals in caudate nucleus or putamen were observed compared with controls.

Anecdotal case reports suggest resolution of RLS symptoms and periodic limb movements after pallidotomy and deep brain stimulation (DBS) in PD patients [50,51]. Aggravation or unmasking of the spinal flexor reflexes due to disinhibition of dopamine-linked systems has also been suggested and opioid and monoamine pathways have been proposed as a unifying hypothesis.

### The iron deficiency hypothesis

The possible relationship between iron deficiency and RLS was hinted at as early as 1672 when Thomas Willis noted that the condition he described was exacerbated by the practice of blood-letting [9]. In 1953, Nordlander proposed that a tissue deficiency of iron was a cause of RLS, and treated 22 patients (including those without iron deficiency) with intravenous iron. He found that 21 patients reported an improvement in symptoms lasting several months [52,53]. Brain iron deficiency is thought to be characteristic of early-onset RLS (symptoms

first occurring in patients aged <45 years), but not of late-onset RLS (symptoms first occurring in patients aged  $\geq 45$  years).

Allen and colleagues investigated iron status in RLS patients using various methods, including magnetic resonance imaging (MRI) paradigms to measure regional brain levels of iron, cerebrospinal fluid (CSF) levels of ferritin and transferrin, serum levels of ferritin, and *post mortem* measures of cerebral iron levels and iron regulatory proteins [54,55]. However, MRI has limitations in detecting altered iron metabolism; whilst it provides information on ferritin-bound iron, the total tissue iron cannot be determined, nor can the site and availability of the iron. In a *post mortem* study comparing brains of RLS patients with those of controls, H-ferritin staining in the substantia nigra was significantly reduced, as was ferritin and transferrin receptor staining in neurons containing neuromelanin. Furthermore, total iron regulatory protein (IRP) activity, specifically IRP1 activity, was significantly decreased in the neuromelanin cells of patients with RLS, suggesting defects in the post-transcription regulatory mechanism for transferrin receptor expression [56]. This could form the basis of a mechanism for cellular iron deficiency.

More recently, a novel hypothesis has been suggested on the basis of reduced Thy-1 expression in the substantia nigra of RLS patients. Thy-1 is a cell adhesion molecule involved in regulating vesicular release of neurotransmitters. Thy-1 concentrations are decreased in cell and animal models by iron chelation; thus, the novel concept of compromised dopaminergic neurotransmitter release due to iron deficiency was proposed [57,58].

Using transcranial sonography, Schmidauer et al. have reported reduced midbrain echogenicity in RLS patients



compared with controls and PD patients, further supporting the role of iron in RLS (Fig. 3) [59].

A number of medical conditions associated with iron deficiency, such as pregnancy, and uremia/dialysis can cause secondary RLS, and have helped to highlight a possible role for iron in this illness. However, this hypothesis does not explain the following:

- Many RLS patients have normal iron status.
- RLS is not universal amongst iron-deficient patients.
- Oral iron replacement does not satisfactorily control RLS symptoms in many patients.

### The role of the opioid system

Opiates are known to be beneficial in the treatment of RLS, suggesting a possible involvement of  $\gamma$ -aminobutyric acid (GABA) and serotonergic pathways in the pathogenesis of RLS [60]. The opioid pimozone appears to block the beneficial effect of dopamine agonists in RLS, suggesting that opiates may also be active via the dopaminergic system [60]. Using  $^{11}\text{C}$ -diprenorphine PET studies, von Spiczak et al. reported a greater increase in the release of endogenous opioids as the severity of RLS symptoms increased [61]. There is therefore some circumstantial evidence to implicate opiate neurotransmission in the pathogenesis of RLS.

### Conditions associated with RLS (secondary RLS)

A number of neurological, pharmacological, and medical conditions are associated with RLS. The best known include pregnancy, iron deficiency and uremia/dialysis, PD, and PLM, and these have helped to highlight several possible etiologies for RLS [62,63].

#### Pregnancy

During pregnancy, 11–27% of women in western countries experience symptoms of RLS, often during the third trimester [64]. Manconi et al. found that pregnant women affected by RLS presented with lower hemoglobin levels and smaller mean corpuscular volumes than those unaffected, despite both groups taking iron and folate supplements [65]. Symptoms normally resolved around the time of delivery. In patients with pre-existing RLS, symptoms were often exaggerated during pregnancy, particularly during the third trimester.

#### Uremia and renal dialysis

Reports on the rate of RLS in patients receiving renal dialysis suggest a prevalence of 6.6–62.0%, and an increased mortality rate has been reported in those with end-stage renal disease and RLS [66]. This wide range may be accounted for by different methods of diagnosis, small cohorts, and ethnic diversities in the populations studied [67]. The pathogenesis

of RLS in patients with end-stage renal failure is unclear, and there are many confounding factors in such patients, including pruritus and peripheral neuropathy, which may not be distinguishable from RLS in those studies where IRLSSG-validated criteria were not used. However, in a cohort studied by Winkelmann et al. of hemodialysis patients diagnosed with RLS according to the IRLSSG criteria, all patients with functioning transplants reported an immediate dramatic improvement in RLS symptoms. There appeared to be a correlation between RLS symptoms and function of the transplanted kidney among patients who remained contactable for long-term follow-up [68].

#### Parkinson's disease

The association of RLS and PD remains controversial as misdiagnosis can occur due to nocturnal dyskinesias and akathisia in PD patients receiving dopaminergic drugs. Observational studies suggest a RLS prevalence of approximately 20% in PD patients [69,70], almost twice the rate of in the general population. The theory of association is strengthened by the consistent response of RLS symptoms to the dopaminergic drugs used in PD. However, there is little evidence to suggest that RLS may precede the development of PD except in a few anecdotal case report based studies [50,51].

#### PLM disorder

Although RLS is primarily a sensory disorder, it has been associated with the motor disorder PLM. PLMs in sleep are not specific to RLS, but occur in 80–85% of RLS patients, and correlate with clinical ratings of RLS severity. PLMs are repetitive stereotyped movements of the lower limbs that occur approximately every 5–90 s during sleep or at rest while lying down. They resemble the flexor withdrawal reflex, with dorsiflexion of the toes and ankle and partial flexion of the knee and sometimes hip. PLM remains a laboratory diagnosis and not a specific disorder. PLM disorder was first described as nocturnal myoclonus by Symonds in 1952 [11], and in 1982 Coleman developed scoring criteria from polysomnographic recordings [71]. These criteria have since been adapted by the American Sleep Disorders Association, and most recently reconsidered by the World Association of Sleep Medicine (WASM) [72,73]. The most commonly used tool for expressing the frequency of PLM is the PLM index, calculated as the number of PLMs/h of sleep time. A PLM index  $>5/h$  is considered abnormal [74,75], although the exact pathophysiological significance of PLM remains unclear.

The majority of RLS patients experience PLM, with prevalence ranging from 6–58% in subjects aged  $>60$  years [75]. In a polysomnographic study of 133 RLS patients, a PLM index  $>5/h$  was found in 80% of patients

**Table 4.** The most common differential diagnoses of restless legs syndrome [24].

**General disorders**

- Nocturnal leg cramps
- Akathisia
- Burning feet syndrome – small fiber neuropathy
- Nocturnal dystonia in feet or toes
- The syndrome of painful legs and moving toes
- Vascular disease (varicose veins, intermittent claudication)
- Vesper’s curse (a rare condition associated with congestive heart failure causing nocturnal pain in the lower limbs extending to the lumbosacral region)

**Sleep-related disorders**

- Insomnia
- Sleep-onset myoclonus

during a 1-night observation; when the study was extended to 2 nights, 88% demonstrated a PLM index of >5/h [75]. Correlations have also been found between the subjective severity of RLS symptoms and the frequency of PLMs [76,77].

PLMs are also associated with various other sleep disorders and several conditions involving altered dopaminergic function, including rapid eye movement (REM) sleep behavioural disorder (RBD), PD, and Gilles de Tourette’s syndrome, and have therefore been suggested as a putative motor sign of dopaminergic function [77].

There is ongoing debate as to how best to quantify PLMs. WASM recently published new guidelines for recording and scoring PLMs [74]. However, a subsequent paper by Ferri et al. compared the frequency of limb movements in RLS patients and controls using more inclusive criteria for identifying candidate movements, such as a lower amplitude threshold [78]. They found that a significant number of leg movements that would normally fall outside the ranges for inclusion in PLM criteria were increased in RLS patients compared with controls, suggesting that the current criteria are too rigid.

Ferri et al. also derived a new measurement for PLM, the periodicity index, from their observation that intervals between leg movements of <10 s were equally present in RLS patients and controls. The periodicity index divides the number of sequences of >3 movement intervals in 10–90 s by the total number of movement intervals. A periodicity index value of 0 therefore indicates no periodicity, whilst a periodicity index of 1 indicates complete periodicity. This may be useful in qualitatively assessing PLM, and could prove a useful tool for elucidating the underlying biological mechanisms of PLM and how they relate to other features of RLS [79].

**Table 5.** Differences between RLS, akathisia, leg cramps, positional discomfort [24].

**RLS**

- Occurs at rest/sleep
- Dopaminergic drugs used to treat dysfunction
- Usually occurs in lower limbs
- Slow and repetitive movements

**Akathisia**

- Can occur at any time
- Treated with neuroleptics/dopaminergic drugs
- Can occur in face, tongue, upper or lower limbs
- Fast and choreic movements

**Leg cramps**

- Motor restlessness not present
- Usually not relieved by movement (but sometimes movement responsive)
- Visible muscle contraction
- Usually occurs in calf muscle

**Positional discomfort**

- Aching sensation
- May be helped by massaging legs
- No visible muscle contraction
- Frequently asymmetrical

RLS: restless legs syndrome.

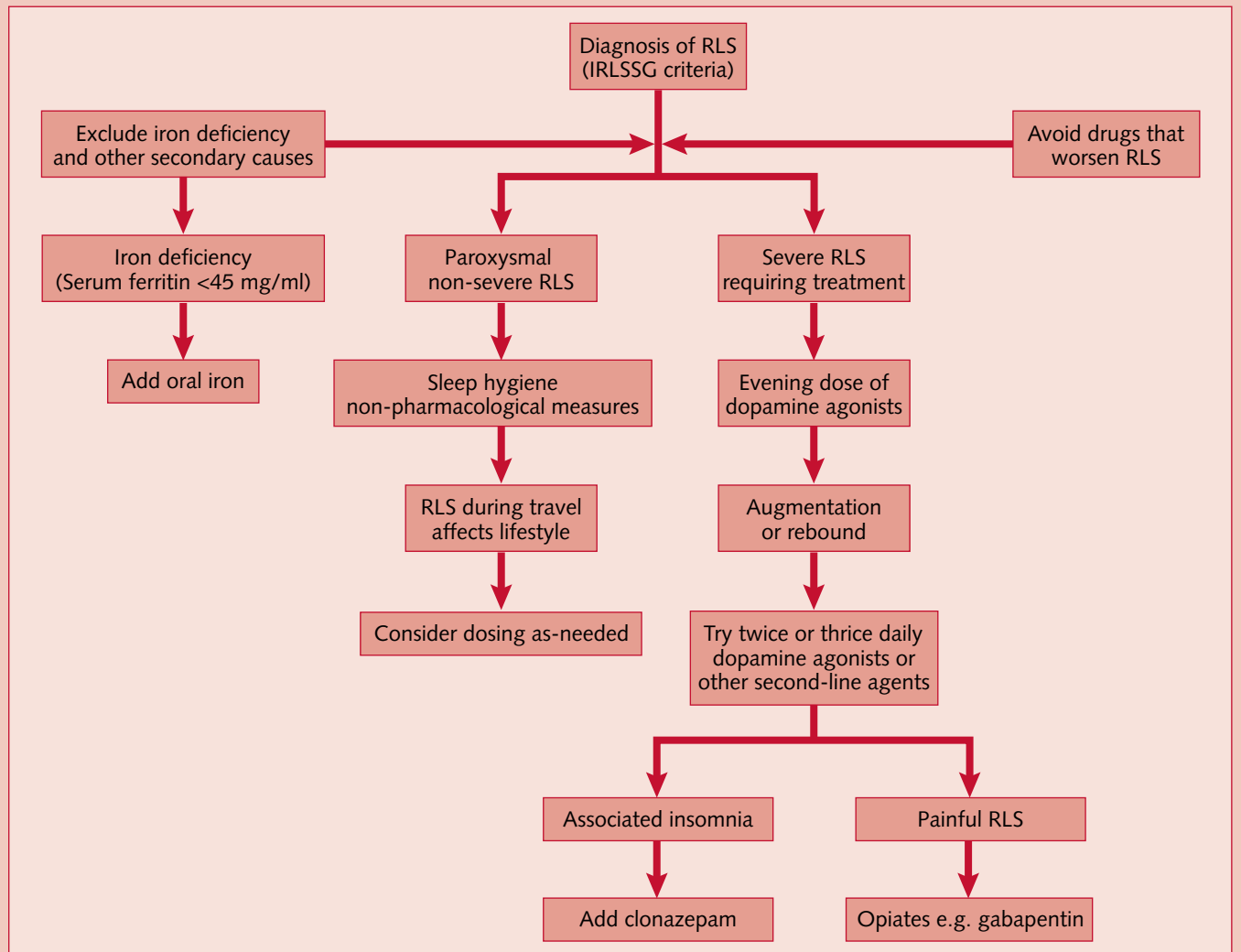
**Neuropathy and RLS**

RLS is associated with axonal neuropathy. Neuropathic RLS patients tend to be older and do not have a family history of the illness [36,80,81]. Neuropathic RLS symptoms may be progressive, although the response to dopaminergic drugs seems to be similar to that of idiopathic RLS. Neuropathic RLS has also been associated with inherited neuropathies such as Charcot-Marie-Tooth disease and uremic neuropathy in renal failure [36,39].

**Clinical course of RLS**

The clinical course of RLS is often chronic and progressive with periodic exacerbations; however, neurological examinations appear normal except in cases of concomitant neuropathy [24,36]. It is difficult to assess the true natural history of RLS as clinical samples providing such information are generally likely to be progressive and severe. Neuropathic RLS and RLS presenting in older age groups appears to be progressive. In some patients RLS occurs as symptom clusters appearing for a few days and then disappearing over a period of time.

Figure 4. An algorithm for the treatment of RLS [83].



IRLSSG: International Restless Legs Syndrome Study Group; RLS: restless legs syndrome.

## Differential diagnoses

RLS is not just simple restlessness of legs, “twitchy limbs” or “fidgetiness”. Positional discomfort and akathisia often cloud the diagnosis of RLS and a list of the differential diagnosis of RLS is provided in Table 4.

The most common differential diagnoses include nocturnal leg cramps, akathisia, and positional discomfort, while nocturnal dystonia, vascular disease, and Vesper’s curse are rarer. Leg cramps are not associated with motor restlessness and there is usually no relief upon moving the limb. Distinguishing RLS from akathisia and positional discomfort can be more difficult, and a number of differences are outlined in Table 5.

## Laboratory investigations

Obtaining a diagnosis of RLS relies on an accurate clinical history from the patient and partner if necessary. Data

on the levels of ferritin in RLS patients is essential, and other tests may need to be performed depending on clinical relevance. These include investigations to rule out secondary or reversible causes such as diabetes mellitus, hypothyroidism, and renal failure.

Polysomnography (PSG) is rarely indicated in RLS patients, except for in those with persisting sleep disturbances despite optimal treatment, or for conformation of a diagnosis of PLM. Occasionally, PSG can also identify undiagnosed sleep-disordered breathing or RBD, which may coexist with RLS [32,82]. Actigraphy and immobilization tests are also used for assessing increases in PLM, but these are restricted to specialized laboratories.

## Management of RLS

A summary/algorithm for the treatment of RLS is provided in Figure 4 [83]. Treatment strategies for RLS range from

**Table 6.** Drugs that may worsen restless legs syndrome

Some antidepressants
Calcium channel blocking antihypertensives
Antiemetics (except domperidone)
Excessive consumption of caffeine in coffee, tea, chocolate, or fizzy drinks
Phenytoin
Alcohol close to bedtime

general measures to pharmacological treatment [84]. Only 20–25% of RLS patients have symptoms severe enough to warrant pharmacological treatment, and confirmation of the diagnosis and reassurance about the condition may be all that is required for the majority of patients. Several factors, including patient age, disease severity and symptom frequency (cluster versus constant RLS), pregnancy, comorbidities such as cardiac disease, and possible effect on occupation (i.e. fear of traveling), can influence the choice of treatment [24].

Patients with milder symptoms may respond well to non-pharmacological measures such as improved sleep hygiene and avoidance of aggravating factors like caffeine, alcohol, stimulants, some antidepressants, and smoking. It is important to differentiate between idiopathic and secondary RLS and to treat the underlying cause if reversible. In iron deficiency, oral iron supplementation should be given before starting other treatments.

Self-help measures may help patients to cope with the symptoms of RLS. Measures are aimed at distracting the patient's mind from the symptoms and include:

- Walking and stretching.
- Hot/cold baths.
- Massaging affected limbs.

It is also important to ensure that patients are not taking drugs that worsen RLS symptoms (Table 6).

### Pharmacological treatment

There is good evidence supporting the use of dopamine agonists as first-line pharmacological treatment for patients with RLS [24,84]. Ergot and non-ergot agonists are effective, and the non-ergot agonists ropinirole and pramipexole have recently been licensed in the US and the UK for the treatment of primary RLS [85]. Previous to the advent of dopamine agonists, levodopa was considered the gold standard for RLS treatment; however, its use has been limited by the emergence of complications such as augmentation and rebound [16].

**Table 7.** Recommended doses for drugs used to treat restless legs syndrome.

Drug	Dose
<b>Dopamine agonists</b>	
Pramipexole (not yet licensed in the US)	0.125–0.75 mg/day (salt preparation)
Ropinirole	0.25–4 mg/day
Cabergoline	0.5–2 mg/day (single evening dose)
Pergolide	0.1–0.75 mg/day or twice daily
Apomorphine	18–50 mg/12 h Overnight subcutaneous infusion
Rotigotine	Dose to be decided after trial
Levodopa DCI	100–600 mg evening or divided dose
<b>Non-dopaminergic treatments</b>	
Gabapentin	300–1800 mg/day
Carbamazepine	100–600 mg/day
Oxycodone	2.5–25 mg/day
Tramadol	50–100 mg/day
Clonazepam	0.5–2 mg evening dose
Triazolam	0.125–0.25 mg/day
Nitrazepam	2.5–10 mg/day
Clonidine	0.15–0.9 mg/day
Iron sulphate	200 mg twice daily (oral)

### Dopamine agonists

Dopamine agonists have recently been considered the first-line therapy for treatment of RLS and PLM disorder [24,85], and are effective in relieving the nocturnal and wake-state symptoms of RLS. The majority of dopamine agonists are effective, and a dramatic response to night-time doses of these drugs has been reported. Recommended doses for the treatment of RLS are much lower than those for PD patients (Table 7).

Doses are generally titrated upwards according to clinical response. Side effects include nausea and vomiting, nasal stuffiness, and rarely, postural hypotension. There is growing evidence that ergot derivatives may be associated with a small risk of pleuropulmonary fibrosis [86]. Non-ergot dopamine agonists have been noted to contribute to sudden sleep onset, but this was reported in PD patients where higher doses of these drugs were used.

### *Pramipexole*

In placebo-controlled trials, pramipexole (0.125–0.75 mg/day of the salt preparation) improved symptoms of restlessness and PLM at night and during the day, but showed no effect on sleep [87]. The efficacy of pramipexole was also reported in a recent large European multicenter study and in a 6-month controlled withdrawal study [88,89]. Montplaisir et al. reported continued efficacy of pramipexole (0.25–0.75 mg evening dose/day) during 8 months of follow-up and improvements in both sensory and motor function after treatment [90]. Pramipexole may also be useful for treating depression and low mood; these associations are currently being explored in RLS [91].

### *Ropinirole*

The largest European trial investigating the efficacy of ropinirole (TREAT-RLS study) involved 284 patients in a 12-week, randomized, double-blind trial, and confirmed the superiority of ropinirole over placebo [92]. In another large, US-based, randomized, double-blind, 12-week clinical trial of 381 patients, ropinirole improved subjective measures such as sleep, quality-of-life, and anxiety [93]. Both studies confirmed that ropinirole is generally well-tolerated. An open, randomized, crossover trial of ropinirole versus controlled-release levodopa in chronic hemodialysis patients also showed significantly greater improvements in RLS severity and sleep time with ropinirole [94].

### *Rotigotine and apomorphine*

Rotigotine transdermal patches (size 2.5 cm<sup>2</sup>/1.125 mg) are currently undergoing clinical trials for use in RLS patients. In a controlled trial involving 63 patients, rotigotine (4.5 mg) significantly reduced RLS severity scores compared with placebo [95]. Apomorphine has also been shown to be effective in treating severe and refractory idiopathic RLS. This may be due to its dopaminergic or opiodergic activity; however, apomorphine is not widely available or specifically indicated for RLS [96].

### *Bromocriptine and pergolide*

Pergolide is the most studied of the two ergot derivatives and produced sustained symptom relief throughout the night when given as a single or divided dose (0.1–0.75 mg) [97]. Further analyses have shown a greater improvement in PLMs when pergolide (0.125–0.25 mg/day) was compared with levodopa (250–500 mg/day); 79% vs. 44.5%, respectively [97]. The PEARLS (Pergolide European Australian RLS study) also demonstrated that pergolide improved symptoms of PLM and sleep disturbance, and was well tolerated [98]. Bromocriptine was the first dopamine agonist to be used for treating RLS and has been shown to have similar therapeutic

effects to pergolide in a comparative study with levodopa; however, levodopa was better tolerated [15].

### *Cabergoline*

Evidence from controlled trials has demonstrated the efficacy and tolerability of cabergoline in the treatment of RLS [99,100]. Cabergoline has the added advantage of a long half-life and, thus, can be given as a once-daily dose to cover daytime and night-time symptoms. Stiasny-Kolster et al. reported continued efficacy at 1 year follow-up with cabergoline (0.5, 1.0, and 2.0 mg/day), and there was a marked improvement in symptom severity compared with placebo [99]. However, recent reports of ergot-related fibrotic side effects, particularly cardiac valvular fibrosis in PD patients, would suggest caution in the use of ergot dopamine agonists.

### *Levodopa*

Levodopa is no longer a first-line treatment for RLS; however, it is effective for nocturnal symptoms of RLS and PLM disorder as demonstrated by several studies using single evening or divided doses (100–600 mg). Its use is limited by the emergence of side effects such rebound and augmentation [15,16,101].

## **Non-dopaminergic treatments**

### *Anti-epileptics*

Evidence from open-label and double-blinded trials show that gabapentin and carbamazepine are effective in treating the sensorimotor symptoms of RLS [102]. In a study comparing gabapentin and ropinirole in the treatment of idiopathic RLS, PSG studies showed a decrease in PLM in both groups that was present at 6-month follow-up in the majority of patients [103]. Happe et al. reported an efficacy and tolerability similar to ropinirole in this trial. Gabapentin is also useful for the treatment of RLS symptoms associated with painful sensations, and some studies have reported beneficial effects in uremic patients and in those receiving hemodialysis [66].

### *Benzodiazepines*

Clonazepam (0.5–4.0 mg) is the most widely used benzodiazepine, although others such as triazolam and nitrazepam may also be useful in treating RLS. Results from double-blinded, crossover studies are variable, reporting either slight or no benefit, but the overall consensus is that clonazepam may be helpful in RLS treatment [24]. Clonazepam has been successfully used in the treatment of RBD [104], which may co-occur with RLS. In addition, benzodiazepines may help with RLS-associated insomnia. The main side-effects associated with this drug group are

respiratory depression, dependence, and disruption of sleep architecture. The efficacy of newer benzodiazepines such as zopiclone has yet to be established. Caution must be exercised with long term use of benzodiazepines as they can cause cognitive problems such as forgetfulness and daytime somnolence.

### Opioids

The use of opioids for conditions similar to RLS began as early as the 17th century [61]. Oxycodone and propoxyphene have been reported to be effective for RLS and PLMS in controlled trials [105]. Strong opioids such as methadone, levorphanol, and morphine are generally only recommended for severe RLS cases that do not respond to other treatment [106].

### Adrenergic drugs

This class of drugs acts by suppressing noradrenergic activity. Clonidine (0.15–0.9 mg/day) and propranolol have been shown to be relatively effective in primary and uremic RLS patients [24,66]. In a randomized, double-blind, placebo-controlled trial, clonidine was reported to be effective for symptoms of RLS, but not PLM disorder [107]. The use of adrenergic drugs is complicated by adverse effects such as depression, insomnia, and hypertensive crises.

### Iron therapy

Oral iron administration is recommended when ferritin levels are below normal or low normal, based on local laboratory ranges (these vary between countries). Iron treatment is often deemed appropriate when ferritin levels are  $\leq 45$   $\mu\text{g/dL}$  [3]. Patients receiving regular iron therapy require monitoring of their iron levels to avoid long-term iron overload. Intravenous iron therapy is currently under investigation and is not routinely clinically recommended [14].

### Complimentary therapies

Anecdotal reports from many patients suggest that complimentary or alternative therapy may be useful in treating RLS [109–111]. Alternative treatments such as nutritional supplements, acupuncture, massage therapy, vibration, and transcutaneous electrical nerve stimulation may be helpful in relieving symptoms of RLS; however, at present, there are no robust trials confirming the effectiveness of these therapies in RLS [111].

### Rebound and augmentation

The rebound phenomenon involves the re-emergence of RLS symptoms at night or early morning. This is usually counteracted by using a controlled-release formulation at night [83]. Augmentation is the earlier onset of symptoms

before the next scheduled dose and is associated with retrograde expansion, an increase in overall severity, faster onset of RLS symptoms at rest, and expansion to upper limbs [16]. It occurs with chronic levodopa treatment and has occasionally been reported shortly after starting therapy. Augmentation has also been reported with dopamine agonist use, and rates vary between 2–30% [24]. An additional afternoon dose maybe useful, and in some cases switching to another dopamine agonist or a non-dopaminergic drug can help. In general, symptoms of augmentation are milder when using dopamine agonists than with levodopa.

### Conclusion

RLS is possibly the most common movement disorder in Western countries and can have a significant adverse effect on patients' lives, both at night and during the day. In the UK and many other countries, it remains under-recognized and misdiagnosed, leaving many patients in considerable distress. Misdiagnosis may also lead to patients with RLS being prescribed sedatives, medications for cramps, and antidepressants, some of which can worsen the symptoms of RLS. The emergence of effective, licensed treatments for this condition shows great potential for improving the quality of life in this group of patients; however, accurate diagnosis is essential.

### Disclosures

The authors have no relevant financial interests to disclose.

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# Sleep-Disordered Breathing in Children

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Sleep-disordered breathing (SDB) is a clinical condition whose symptoms range from primary snoring to severe obstructive sleep apnea (OSA). This syndrome can manifest at any age, but is predominantly seen in preschool and early elementary school age children – a time period that coincides with adenotonsillar hypertrophy. In children, the prevalence of snoring without OSA is approximately 15%, while the prevalence of OSA in children is estimated at 5%. Snoring should not be accepted as normal in children. Significant SDB may be present even in the absence of parental reports of loud snoring. Children with SDB are more likely to have behavioral problems such as hyperactivity and emotional lability. Other symptoms may include excessive daytime sleepiness, bedwetting, parasomnias, and restless or non-refreshing sleep. A diagnostic polysomnogram is helpful but not always necessary prior to treatment, which is most commonly adenotonsillectomy. Residual symptomatic SDB may require other treatments such as positive airway pressure, orthodontics, nasal steroids, or further surgery. *Int J Sleep Disorders* 2006;1(2):55–60.

Pediatric sleep medicine has evolved into a major area of study [1]. One of the most important conditions in this field is sleep-disordered breathing (SDB), a clinical syndrome that can manifest at any age and whose symptoms range from primary snoring to potentially life-threatening obstructive sleep apnea (OSA) syndrome. The syndrome is particularly common in preschool and early elementary school age children. This time period coincides with peak adenotonsillar hypertrophy. Many clinicians have become familiar with OSA in adults but are less experienced with regard to children. Table 1 compares adults and children with this syndrome. Historically, OSA was first recognized from the study of Pickwickian syndrome. However, it is important to highlight that in *The Posthumous Papers of the Pickwick Club*, the classic description of snoring with arousals and excessive daytime sleepiness was not of the adult Mr Pickwick, although he probably did have OSA, but was of a boy, Joe, who constantly fell asleep in any situation regardless of the time of day. The first medical description in English of children with abnormal breathing in sleep is attributed to William Osler in his 1892 textbook, *Chronic Tonsillitis* [2]. Osler wrote a dramatic description of the condition, and hypothesized that chronic enlargement of the tonsils causes sleep disturbance in children.

In modern medical literature, Guilleminault reported the first series of children with OSA in 1976, and described the essential clinical features of this condition [3]. Eight children

aged 5–14 years were diagnosed using nocturnal polysomnograms. Guilleminault wrote that excessive daytime sleepiness, decrease in school performance, abnormal daytime behavior, enuresis, morning headache, abnormal weight, and progressive development of hypertension suggest the possibility of a sleep apnea syndrome when any of these symptoms is associated with loud snoring interrupted by pauses during sleep. Surgery was advocated to eliminate the symptoms.

More recently, there has been a realization that patients may be symptomatic in the absence of frank apneas [4,5]. This has led to use of the term “sleep-disordered breathing” to better describe the clinical spectrum, which includes OSA syndrome, upper airway resistance syndrome, and obstructive hypopnea syndrome.

## Symptoms of SDB

### Snoring

The most obvious nocturnal symptom of SDB is snoring. Snoring indicates turbulent airflow and is not normal in children [6–11]. The American Academy of Pediatrics has recommended all children should be screened for snoring as part of well-child care [12]. Not all snoring is caused by OSA; other forms of obstruction such as nasal allergies or a cold could be responsible [13,14].

The prevalence of SDB in children was studied by Rosen et al. who performed a cross-sectional study in a cohort of school-aged children from Cleveland (OH, USA) [15]. The study group consisted of 829 children aged 8–11 years, all of whom had unattended in-home overnight cardiorespiratory sleep recordings. SDB was defined by

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**Table 1.** Comparison of SDB between adults and children.

Factor	Adults	Children
Symptoms	Sleepiness, fatigue, nocturia	Behavioral problems, learning difficulty, nocturnal enuresis
Gender	More common and severe in males	No difference prior to puberty
Physical findings	Obese, large neck circumference, wide tongue, blood pressure elevation	High arched palate, enlarged tonsils, orthodontic problems, less likely to be obese, failure to thrive, sleep with neck extended
Apnea duration	10 s	Two breaths
Diagnostic criteria	AHI >5	AHI >1
Primary treatment	Positive airway pressure	Adenotonsillectomy
Alternative treatment	Upper airway surgery, oral appliance	Positive airway pressure

AHI: apnea-hypopnea index; SDB: sleep-disordered breathing.

either parent-reported habitual snoring or objectively measured OSA. Forty (5%) children were classified as having OSA (median apnea-hypopnea index [AHI] 7.1/h), and another 122 (15%) had primary snoring without OSA. The remaining 667 (80%) had neither snoring nor OSA. Functional outcomes were assessed using two parent-rating scales of behavioral problems; the Child Behavioral Checklist and the Conners' Parent Rating Scale-Revised: Long. Children with SDB had significantly higher odds of elevated problem scores in the domains of externalizing, hyperactivity, emotional lability, oppositional, aggressive, or internalizing behaviours, somatic complaints, and social problems. The authors concluded that children with relatively mild SDB, ranging from primary snoring to OSA, have a higher prevalence of problem behaviors; the strongest and most consistent associations being with externalizing and hyperactive-type behaviors. An interesting finding in this study was that only 55% of the parents of children diagnosed with OSA using a polysomnogram reported loud snoring. If pediatricians and surgeons screen for OSA by asking the parents/caregiver if the child snores loudly, they may miss nearly half of the cases [16].

### Daytime symptoms

While SDB in children has many important similarities to the adult version of this disease, there are also marked differences in presentation, diagnosis, and management. Abnormal daytime sleepiness may be recognized more often by school teachers than by parents of young children. An increase in total sleep time or an extra long nap may be considered normal by parents. Non-specific behavioral difficulties are also often mentioned to the pediatrician such as abnormal shyness, hyperactivity, developmental delays, or rebellious or aggressive behavior [17]. Chervin et al.

found that conduct problems and hyperactivity are frequent among children referred for SDB. They surveyed the parents of 872 children aged 2–14 years at two general clinics between 1998 and 2000. Bullying and other specific aggressive behaviors were, in general, reported 2–3 times more frequently among children at high risk for SDB [18]. Other daytime symptoms included speech defects, poor appetite, or swallowing difficulties [4,19]. Nocturnal enuresis or bedwetting accidents should also raise the question of possible SDB [20].

Many children with SDB mouth-breathe; hence, regular mouth-breathing should always cause suspicion of SDB [21]. Children with SDB may avoid going to bed at night due to hypnagogic hallucinations and morning headaches, dry mouth, confusion, or irritability are often reported upon waking. As mentioned, daytime sleepiness may not be obvious depending on the age of the child, and can translate only as a complaint of daytime tiredness. It may also present itself as a tendency to take naps easily anywhere.

In schools, tiredness and sleepiness can be labeled as "inattentive in class", "daydreaming", and "not being there" [26,27]. Concerns about school performance were raised in the original description of OSA in children [3]. More recently, the possible association between SDB, learning problems, and attention deficit-hyperactivity disorder (ADHD) has been investigated [8,26–34]. A study by Gozal and colleagues examined the hypothesis that domains of neurobehavioral function would be selectively affected by SDB [26]. They studied children aged 5–7 years from a public school system with documented symptoms of ADHD, and determined the incidence of snoring and other sleep problems. Frequent and loud snoring was reported for 673 (11.7%) children, and 418 (7.3%) children had hyperactivity/ADHD. Children with reported symptoms of

ADHD and control children were randomly selected for an overnight polysomnographic assessment and a battery of neurocognitive tests. Eighty-three children with parentally reported symptoms of ADHD and 34 control children were invited for sleep studies. After assessment using the Conners' Parent Rating Scale, 44 children were designated as having "significant" symptoms of ADHD, 27 as having "mild" ADHD symptoms, and 39 were classified as having "none" (controls). Overnight polysomnography indicated that OSA was present in 5% of those with significant ADHD symptoms, 26% of those with mild symptoms, and 5% of those with no symptoms. The authors concluded that an unusually high prevalence of snoring was identified among the group of children designated as exhibiting mild symptoms of ADHD, based on the Conners' Parent Rating Scale. SDB can lead to mild ADHD-like behaviors that can be readily misconceived and potentially delay diagnosis and appropriate treatment [26].

### Clinical signs of SDB

Clinical signs of SDB include increased respiratory efforts such as nasal flaring, supra-sternal or inter-costal retractions, abnormal paradoxical inward motion of the chest during inspiration, and sweating during sleep. The sweating may be limited to only the nuchal region, particularly in infants, and can be severe enough to necessitate changing clothes during the night. Parents may mention that the child feels warm at night or prefers to sleep without a blanket, and also observe that the child stops breathing and then gasps for breath. However, despite the observation of abnormal breathing patterns by parents, a surprisingly high number are never questioned about this by pediatricians during regular visits.

Information regarding the sleep position is also helpful in determining SDB. Typically, the neck is hyper-extended and the mouth is open. Another typical sleeping position is prone with the knee tucked under the chest and the head turned to the side and hyper-extended. Children with SDB generally prefer to sleep without several pillows [4].

Ohayon et al. found that individuals identified with SDB have a much greater incidence of nightmares, with reports of "drowning", "being buried alive", and "choking" [35]. SDB leads to sleep fragmentation or disruption, and any condition that disturbs slow-wave sleep can cause sleep terrors and sleepwalking in children [36]. A child with parasomnias should be evaluated for SDB as these can be triggered or exacerbated by interrupted sleep.

A physical finding that may be overlooked in a child with SDB is a narrow and high-arched palate [4]. Interestingly, the description of ADHD in the Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV) mentions that minor physical anomalies such as high-arch palates may be

present [37]. As both conditions can exhibit similar daytime behavior in the same age group, a child with SDB may be misdiagnosed as having ADHD. The possibility of a sleep disorder being present should therefore be considered in any child being evaluated for ADHD. This is particularly important as treatment of SDB can improve behavior and academic performance [38,39].

### Diagnosis of SDB in children

The diagnostic criteria used for adults with OSA cannot be used reliably in children [5,21,40,41]. Diagnosis of SDB is based on history, physical findings, and supportive data. Laboratory testing should ideally be tailored to the clinical question; for example, if there are concerns about excessive daytime sleepiness, a multiple sleep latency test (MSLT) may be indicated [42]. The MSLT is best performed in subjects  $\geq 8$  years old.

Polysomnograms performed in a child use the same technology and record the same information as in adults. Breathing measurements of airflow, respiratory effort, and pulse oximetry are usually monitored. Different techniques, ranging from qualitative methods, such as nasal thermocouples that use the temperature difference between inhaled and exhaled air to measure individual breaths, to quantitative and invasive measures, such as esophageal pressure values, can be used to measure breathing. The latter technique is less tolerable, but is particularly helpful in distinguishing central from obstructive apneas. End-tidal CO<sub>2</sub> monitoring can help detect transient episodes of hypoventilation. Currently, measuring airflow using a nasal pressure cannula balances the need for quantification with tolerability [43,44]. This technique allows for the identification of more subtle breathing episodes, but can be harder to interpret than earlier techniques, particularly when a child is mouth breathing.

The multitude of techniques available to measure breathing makes it difficult to compare the results from different studies. Along with the absence of controlled studies, a significant problem in evaluating SDB in children is the variation in the definitions for key terms. In adults, OSAs are defined as lasting  $\geq 10$  s. However, since children have a faster respiratory rate than adults, a clinically significant apnea can occur in a shorter period. Apneas as brief as 3–4 s may cause oxygen desaturation. Therefore, sleep apnea in children is defined as an interruption of airflow for  $\geq 2$  respiratory cycles. There is no universally accepted definition of hypopneas in children, but specialists tend to consider this as a reduction of  $\geq 50\%$  of airflow, associated with hemoglobin desaturation or awakening. The most recent edition of the *International Classification of Sleep Disorders* defines sleep apnea in children as an

AHI>1 [45]. In adults, an AHI>5 is required. Unfortunately, it is not uncommon for an adult cut-off value to be used in children [46].

The nasal pressure cannula has facilitated measurement of respiratory event-related arousal (RERA). The respiratory disturbance index (RDI) includes the total number of apneas, hyponeas, and RERAs divided by the total sleep time and should be distinguished from the AHI. However, some sleep study reports may equate the RDI with the AHI if the study did not measure RERAs. The clinician needs to be aware that these terms can be used interchangeably, potentially causing confusion.

Controversy exists over whether a diagnosis of OSA, or the larger spectrum of SDB, should be routinely made without a formal polysomnogram. Some physicians have suggested that this diagnosis can be made in patients using clinical history and physical examination either alone, or in combination with an audio or videotape of the child sleeping. Others have found an inability of clinical history alone to distinguish primary snoring from OSAS in children [47]. This is further complicated by the description of more subtle events such as RERAs, which may have been missed in previous studies. A sleep study is therefore the most definitive test for SDB [48,49]. Currently, a number of otolaryngologists who treat SDB in children may make a surgical recommendation based on clinical findings of airway obstruction, and sometimes by reviewing an audio or video tape [50,51]. Further controversy exists concerning the value of performing a sleep study in an attended sleep laboratory setting compared with allowing the child to sleep in their own bed with an ambulatory sleep study. Clinicians must be aware of the potential pitfalls of these different options. If the sleep study is performed in an attended laboratory setting, the staff must be trained in how to work with children. The bedroom should be able to accommodate a parent or other adult who will accompany the child, with a ratio of one technologist per child being monitored. Children typically sleep longer than adults, and therefore the longer recording time must be taken into account. SDB events tend to cluster during rapid eye movement (REM) sleep in the last third of the night or early morning. The child should be allowed to awake spontaneously, since if the sleep study is terminated abruptly and the child is forced to wake up earlier than usual, the true severity of the SDB maybe underestimated.

There are certainly individual cases where a diagnostic sleep study is not available, but ideally these should be the exception. The challenge faced in sleep medicine is providing easily accessible and cost-effective care while working within a multi-disciplinary model. The accuracy of clinical diagnosis is not known without objective testing. Until there is a better answer, the diagnostic gold standard

should not be disregarded, particularly in a tertiary care setting. The American Thoracic Society, American Academy of Sleep Medicine, and the American Academy of Pediatrics all support the use of sleep studies [48,52,53].

SDB may not be the only sleep disorder present in a child, and clinical impression can result in misdiagnosis and even unnecessary surgery. For example, without confirmatory testing, a child with symptomatic periodic limb movements could be misdiagnosed with SDB and may undergo needless surgery. Periodic limb movements in sleep and restless leg syndrome in children may not be as rare as previously thought, and can be difficult to ascertain [54].

### Syndromes associated with SDB

SDB occurs more frequently in specific populations [55–59]. Any condition with related craniofacial anomalies can be associated with SDB, such as Pierre Robin, Apert's, and Crouzon's syndromes. Approximately half of all children with Down's syndrome suffer SDB. However, symptoms of daytime sleepiness and sleep disruptions at night may be due to non-neurological factors, such as maxillofacial abnormalities, large tonsils or adenoids, hypognathia, or large tongues. Sleep disorders often occur in patients with neuromuscular disorders due to a weakness in the respiratory muscles that is further exacerbated by hypotonia during sleep. In disorders such as Duchenne's muscular dystrophy, daytime pulmonary function studies do not predict the degree of apneic events during sleep. Rather, patients can have nocturnal oxygen desaturation, significant sleep fragmentation, recurrent hypoventilation, and reduced REM sleep, and are also at increased risk for aspiration during sleep. Diagnosis and treatment of SDB in these patients can be an important part of comprehensive management.

### Treatment of pediatric SDB

In addition to the differences in diagnostic criteria between children and adults, treatment options are also distinct. SDB in adults has four treatments options that can be combined. The most common treatment in adults is continuous positive airway pressure (CPAP) to help splint open the upper airway. When CPAP is used correctly, snoring during sleep should be absent. There are also several sophisticated surgical options that have a wide range of success. In adults, oral appliances that help to re-position the mandible have improved breathing during sleep in select patients. As a conservative measure, adults with SDB are advised to sleep off their backs, lose weight, and avoid alcohol before sleeping.

Unlike in adults, surgery is most frequently recommended for initial treatment of SDB in children. Adenotonsillectomy is most common, and this procedure can be extremely effective

and result in dramatic improvements. When surgery is considered, it is recommended that the adenoids and tonsils should both be removed. It is tempting in very small children to only remove the adenoids if the tonsils do not appear overly enlarged, as this allows for less post-operative pain and a lower risk of adverse events such as bleeding. However, this practice should be discouraged as even though the tonsils do not seem enlarged, the surgeon must remember that they are examining a child that is awake and sitting. The relative posterior airway space may be obstructed when the child is supine, with the tongue falling back and the airway narrowing during REM sleep hypotonia. Also, as a child grows, the tonsil size may increase. If the adenoids alone are removed, there is a risk of the child having to later return for further surgery to remove the tonsils. The anesthesiologist should also be familiar with sleep apnea as pulmonary complications can occur post-operatively [60].

Children with sleep apnea are often thinner than expected. This can be due to multiple factors, including the greater calorific demand of breathing through a narrow airway and possible disruption of growth hormone secretion; hence, children may experience weight gains after sleep apnea surgery [61].

Surgery does not always completely cure the child's SDB, and the true cure rate is not known [22,62–64]. Most analyses of post-surgical sleep studies have used older adult definitions of sleep apnea in the children. Suen and colleagues designed a prospective study of 69 children aged 1–14 years who were referred to an otolaryngologist [65]. Thirty-five (51%) of the children had an RDI>5 on polysomnography. Of these, 30 underwent adenotonsillectomy and 26 had follow-up polysomnography. All 26 children had a lower RDI after surgery, although four patients still had an RDI>5. Using an RDI cut-off of 5, the cure rate of surgery would be 85%. However, three children were found to continue snoring with a post-operative RDI<5. If those patients are considered to have residual SDB, then the cure rate of surgery would only be 73%. Hence, all patients were found to improve with adenotonsillectomy, but the true cure rate is not clear. The possibility of residual SDB should always be considered after surgery if the child remains symptomatic. Clinical history and physical findings were not useful in predicting outcomes following surgery [65]; however, different surgical techniques may improve the success of surgery in these children [66].

It could be argued that sleep studies are not required in clear cases of SDB. However, the adult experience teaches us that it is precisely these obviously more severe or “clear cut” cases who are most likely to have residual disease. Adenotonsillectomy does not change tongue size and shape relative to the palate. The parents may report that the child

is “100% better”, and yet an obstruction could still remain. If no post-operative sleep test is performed, a residual sleep problem may be overlooked or no longer considered a possibility, and if the child still has trouble paying attention in school, they could be misdiagnosed as having ADHD [7,67].

If surgery is not a viable option for a child then CPAP therapy should be considered [68–70]. CPAP uses a small air compressor attached to a mask via a hose. The mask usually only covers the nose, although masks are available that cover both the nose and mouth. By forcing positive pressure into the airway, the negative pressure of inspiration can be countered to avoid airway narrowing or collapse. CPAP is effective but can be cumbersome to use; however, the CPAP devices have become smaller and quieter and are available in several styles and sizes. Although previously available in other countries, positive airway pressure devices have been only recently approved for children in the US by the FDA [71]. The FDA specifically approved a bi-level device and mask in children aged  $\geq 7$  years or weighing  $>40$  lbs with respiratory insufficiency or OSA. Despite these advances, CPAP remains a second choice over surgery in most children [48]. The main drawbacks of using CPAP relate to finding a CPAP mask that fits properly. If the mask is not fitted correctly, the air pressure can leak out causing discomfort and disrupting sleep while facial abrasions or bruising can occur if the mask is fitted too tightly. In small children, sleeping with the CPAP mask can interfere with the growth of the maxilla. As the child grows, the CPAP may require adjustments, both in terms of mask size and the amount of pressure delivered to the airway. In addition to a continuous pressure delivery mode, a bi-level mode is available. In this mode, the pressure on expiration is lower than the inspiratory pressure, making the device more comfortable, and may be preferable in patients with neuromuscular weakness. The most recent advance in positive airway pressure has been the development of machines that can adjust the pressure required to keep the airway open on a breath-by-breath basis. These “smart CPAP” units are promising, but are not part of the mainstream treatment of SDB in children at this time [68].

## Conclusion

It is important for clinicians to be aware that SDB and snoring are not normal in children, and difficulty in breathing while asleep can negatively impact on daytime behavior. However, SDB is readily treatable with both surgical and non-surgical options.

## Disclosure

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# CLINICAL REVIEWS

## Commentary and Analysis on Recent Key Papers

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

### SLEEP-DISORDERED BREATHING

#### Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children

Emancipator J, Storfer-Isser A, Taylor G et al.  
*Arch Pediatr Adolesc Med* 2006;**160**:203–10.

Pediatric sleep-disordered breathing (SDB) has a disproportionately high prevalence in children who were preterm. This study evaluated performance on objective assessments of cognitive skills and academic achievement in 835 children with and without a diagnosis of SDB from a community-based sample. The deficits in selective measures of academic abilities, language comprehension, and planning and organizational skills suggest SDB is associated with behavioral morbidity.

It is believed that pediatric sleep-disordered breathing (SDB) affects 2–4% of children, with a higher prevalence seen in certain subgroups such as African-American children and those who were preterm. Since a strong learning foundation is essential during childhood, it is important to evaluate the impact of SDB on a child's cognitive and academic skill.

The study researched children with and without a diagnosis of SDB to determine an association between SDB and deficits in cognitive abilities and achievement. Emancipator et al. also investigated whether preterm children are at a heightened risk for SDB-related cognitive dysfunction because of the increased risk of neurodevelopment disabilities related to early-life hypoxemia and ischemic injury. Lastly, the trial investigated whether the severity of overnight hypoxemia positively correlated with the extent of cognitive deficits.

Children, aged 8–11 years, were assessed during a home visit. Cognitive and academic achievements were assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R), the Kaufman Assessment Battery for Children (K-ABC), and the Continuous Performance Test (CPT). The children then

underwent an at-home sleep study the night after these tests were performed. SDB was defined as an obstructive apnea–hypopnea index of  $\geq 5/h$  and/or an obstructive sleep apnea index of  $\geq 1/h$ ; children must also have been characterized as snoring habitually.

In total, 835 children (mean age 9.5 years, 50% female) were studied; 671 children were classed as non-SDB and 164 SDB. Children were also classified into one of four categories according to preterm status and birth weight (premature with extremely low birth weight  $<1000$  g up to normal birth weight  $\geq 2500$  g).

Results show that in fully adjusted analyses, the SDB group tended to score lower on many of the measures. Significantly lower scores were observed for the PPVT-R and the K-ABC (riddles and triangles subscales only). Children with SDB showed a longer mean reaction time in CPT measures; however, after covariate adjustment SDB was not significantly associated with this measure and response discrimination. These analyses were repeated after stratifying by preterm status to investigate whether the association of SDB with cognitive and achievement skills was stronger in the preterm groups. Preterm children with SDB performed significantly worse on the PPVT-R and the K-ABC achievement and simultaneous global scales, as well as on the riddles and triangles subscales. However, differences in neurocognitive function between the full-term children with and without SDB were not significant after fully adjusting for covariates.

The observed results suggest that children with SDB may have weaknesses in attending selectively to tasks and planning their responses and, over time, this can contribute to more pronounced deficits in accumulated knowledge and academic skills. This data is consistent with an association between mild SDB, including snoring, and selective deficits in verbal comprehension and executive functions. Effects were relatively greater in preterm children, who may be particularly vulnerable to stresses associated with SDB.

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## Long-term changes in behavior after adenotonsillectomy for obstructive sleep apnea syndrome in children

Mitchell RB, Kelly J.

*Otolaryngol Head Neck Surg* 2006;**134**:374–8.

The objectives of this study were to assess the various behavioral symptoms that may accompany obstructive sleep apnea syndrome in children, such as aggression, depression, and hyperactivity, and to document symptomatic changes that may have occurred within 6 months and 9–18 months after adenotonsillectomy. The results revealed a statistically significant improvement in all of these behavioral parameters on long-term analysis.

As earlier studies have suggested, obstructive sleep apnea (OSA) in children can result in behavioral impairments, manifested as excessive daytime sleepiness, hyperactivity, and inattentiveness, to name a few. These can improve after surgical interventions, specifically adenotonsillectomy. Previous studies have broached the above issues rather haphazardly by:

- Examining children whose diagnoses may have been confounded due to lack of polysomnographic (PSG) confirmation.
- A short, rather than extended, follow-up after the adenotonsillectomy to assess behavioral changes.

The authors of the present study take these challenges into account and address the previous limitations by providing PSG confirmation of the OSA, as well as allowing for behavioral assessments before surgery, within 6 months and 9–18 months after surgery.

The results from 23 children were submitted in the final analysis. Mean age was 7.2 years (range 2.5–14.8 years) and apnea–hypopnea index was 14.1 (range 5.2–88.0) preoperatively. All the children underwent adenotonsillectomy and their caregivers were instructed to perform assessments using the Behavior Assessment System for Children before surgery, within 6 months, and 9–18 months after surgery. Preoperatively, clinically significant behavioral impairments categorized as aggression, atypicality, depression, hyperactivity, somatization, and externalizing/internalizing problems were observed in all of the participants. Within 6 months of the adenotonsillectomy, clinically significant behavioral improvements were observed in all behavioral parameters, with only one patient continuing to exhibit depression. Interestingly, the survey completed 9–18 months after surgery – although showing overall improvement when compared with the initial assessment – revealed six clinically significant behavioral impairments.

Based on the above data, one could deduce that adenotonsillectomy can ameliorate the behavioral symptoms associated with OSA in children; however, several limitations of this study confound this notion. Firstly, due to the limited sample size as a result of the low retention rate (53%) and the difficulties in assessing a given age group's behavioral symptoms within this small sample, it would be inaccurate to attribute similar behavioral symptoms to the various age groups. Secondly, as there was no control group, a true comparison cannot be made between those who underwent surgery and those who did not. Thirdly, PSG verification was not performed post-adenotonsillectomy to assess whether residual sleep apnea still existed and the effects this may have had on the behavioral assessments.

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## Serum cardiovascular risk factors in obstructive sleep apnea

Can M, Acikgoz S, Mungan G et al.

*Chest* 2006;**129**:233–7.

This study analyzed results from a series of serum tests predictive for cardiovascular disorders in patients with obstructive sleep apnea (OSA) with an apnea–hypopnea index (AHI) >5, OSA patients with AHI <5, and normal controls. C-reactive protein (CRP) and homocysteine were found to be elevated in both groups of OSA patients. These findings support an association between OSA and cardiovascular disease, and specifically identify increased CRP and homocysteine levels as possible mediators of the increased cardiovascular risk in OSA patients.

Obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular morbidity and mortality; however, the mechanisms that underlie this association remain poorly understood. In order to better interpret the relationship between OSA and cardiovascular disease, this study compared levels of a series of serum markers associated with cardiovascular disease in three subject groups: obstructive sleep apnea (OSA) patients with apnea hypopnea index (AHI) >5 (n=30), OSA patients with AHI <5 (n=32), and normal controls (n=30). The serum risk factors studied included cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, apolipoprotein A-1, apolipoprotein B, lipoprotein A, C-reactive protein (CRP), and homocysteine.

Significant differences in serum marker levels between subject groups were only observed with CRP and homocysteine, with CRP levels being the most strongly



associated with OSA status. CRP was significantly higher in OSA patients with AHI >5 than in the AHI <5 patients, and in both OSA patient groups compared with the controls (both  $p < 0.05$ ). Homocysteine was elevated in the AHI >5 OSA patients compared with the AHI <5 patients and the control subjects.

These findings support an association between OSA and cardiovascular disease, and specifically implicate CRP and homocysteine as potential mediators of the increased cardiovascular risk in OSA. While it may appear from this study that serum CRP levels are likely to be the more important mediators, this is not necessarily the case. It is possible that mild OSA patients are not at an increased risk of cardiovascular disorders and thus, homocysteine elevation may be more closely associated with the risk. In order to better understand these associations, longitudinal studies that track elevations in the potential risk factors and measure whether these increases herald the clinical emergence of cardiovascular disorders are needed.

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### The determinants of the apnea threshold during NREM sleep in normal subjects

Rowley J, Zhou X, Diamond M et al.

*Sleep* 2006;**29**:95–103.

This study determined apnea thresholds in men and pre- and post-menopausal women during non-rapid eye movement (NREM) sleep, and further investigated whether hormone replacement therapy would decrease this threshold in post-menopausal women. The trial design consisted of two protocols: an analysis of a prospectively collected database of subjects who had undergone an apnea threshold protocol, and an intervention study. These data suggest that estrogen and progestin positively influence the apnea threshold and control of breathing during NREM sleep.

Studies have shown that sleep-disordered breathing (SDB) is more prevalent in men than in women, and results from epidemiological investigations have revealed a higher prevalence of SDB in post-menopausal women compared with those who are premenopausal.

In the first protocol, 55 healthy non-snoring individuals (35 women) without evidence of SDB were investigated. Menopausal status was measured using serum levels of estrogen, estradiol, and follicle-stimulating hormone, and subjects were divided into three groups:

- Men (n=20).
- Premenopausal women (n=25).
- Post-menopausal women (n=10).

The second protocol examined the effect of hormone replacement therapy (HRT) on the apnea threshold in six post-menopausal women.

After conducting baseline studies to determine the apnea threshold for each individual, the women received HRT (oral medroxyprogesterone acetate [5 mg/day] and estrogen [1.25 mg/day] for 1 month. The apnea threshold was then re-evaluated 30 days after commencing treatment.

Results from the two protocols showed that, at the apnea threshold, change in end-tidal CO<sub>2</sub> was highest in the premenopausal women (4.6±0.6 mmHg), with no difference between post-menopausal women (3.1±0.5 mmHg) and men (3.4±0.7 mmHg). Determinants of this change included gender and menopausal status. After subjects received HRT for 1 month, the change in end-tidal CO<sub>2</sub> at the apnea threshold increased from 2.9±0.4 mmHg to 4.8±0.4 mmHg ( $p < 0.001$ ).

These results provide further evidence in support of the hypothesis that estrogens and progestins positively influence apnea threshold and breathing control during non-rapid eye movement sleep.

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## INSOMNIA

### Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference

Johnson EO, Roth T, Schultz L et al.

*Pediatrics* 2006;**117**:247–56.

This epidemiological study of insomnia in a sample of US adolescents was undertaken to assess the lifetime prevalence of insomnia, in both its acuity and chronicity, and its relationship to pubertal development and comorbid psychiatric disorders. Interviews conducted with the participants revealed a lifetime prevalence of insomnia of 10.7%, a comorbid psychiatric prevalence of 52.8% in the insomniacs, and a menstrual-related exacerbation.

The biological, cultural, and social changes, which among many others herald the onset of adolescence, have rarely been examined with respect to sleep/wake parameters. These can, in turn, affect cognition, health, conduct, and substance use.

The current study undertook the ambitious task of addressing these issues through interviews conducted with 1014 adolescents, aged 13–16 years, randomly selected from an health maintenance organization (HMO) in the metropolitan area of Detroit, MI, USA. Although the racial composition of these participants was similar to that of the Detroit tri-county area population, its socioeconomic status was exclusive of the extremes. The DSM-IV criteria for chronic insomnia, consisting of difficulties initiating, maintaining, or having non-restorative sleep for a period of  $\geq 1$  month resulting in significant distress or impaired functioning, were utilized alongside a minimum symptomatic frequency of 4 times/week. Moreover, based on the recent National Institutes of the Health State-of-the Science Conference Statement [1], the researchers of the present study categorized insomnia as a disorder in and of itself, relinquishing its past designations as either primary or secondary. A self-administered rating scale and the computerized diagnostic interview schedule for children-IV were utilized to assess for indicators of physical development and depression, respectively. Structured interviews, in lieu of questionnaires, were used to ascertain sleep habits and psychiatric disorders.

Of the 1014 participants engaged in this study, 108 (10.7%) met the indicated criteria for insomnia during their lifetime, with the majority (68.5%) reporting difficulty with initiation of sleep, 26.2% with maintenance, and 48.1% with its non-restorative nature. Of those with a lifetime history of insomnia, 88% also had a current episode. The median age of onset of insomnia was 11 years, with girls reporting a significantly older median age (12 years) than boys (10 years). Interestingly, menstruation conferred a 2.75-fold increased risk for insomnia in girls, even when controlling for depression, and manifested itself solely with difficulty maintaining sleep and non-restorative sleep. Approximately half of those adolescents with a lifetime diagnosis of insomnia had at least one concomitant psychiatric disorder compared with those without; no difference was seen in the chronicity of the insomnia. However, earlier age of insomnia onset was seen in those with a concomitant psychiatric disorder compared with those without (aged 10 years and 12 years, respectively). Recognizing the increased prevalence of delayed sleep phase syndrome in adolescents and its possible conflation with insomnia, the researchers of this study found no statistically significant relationship between the two (based on exclusionary criteria).

As the authors highlight, the limitations of this study include:

- The sample population obtained from an HMO setting, which could potentially exclude the extreme socioeconomic spheres.

- The recall biases inherent in a retrospective analysis.
- The difficulty in separating the complex relationships between insomnia, depression, and menses when using only the DSM-IV diagnosis of major depression and not its myriad counterparts.

1. National Institutes of Health State-of-the-Science Conference Statement  
<http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm>

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### Sex differences in insomnia: a meta-analysis

Zhang B, Wing Y.

*Sleep* 2006;**29**:85–93.

The majority of epidemiological evidence suggests a female predisposition to insomnia. The current study applied meta-analytical methods to investigate sex differences in the risk of insomnia among published epidemiological studies. The results confirmed that women are at an increased risk for developing insomnia.

There is a large body of evidence to suggest that women complain of insomnia more frequently than men. Determining a difference in the risk of insomnia between the sexes may help expand our knowledge of the etiology, pathogenesis, healthcare utilization, and treatment and prognosis of this disorder. This is the first study to use meta-analytical methods to integrate results from the published literature of epidemiological studies in order to investigate sex differences in the risk of insomnia. Further subgroup analyses were also performed to examine whether the effect of gender was universal or moderated by other factors such as age and ethnicity.

A total of 29 papers were included in the overall analysis of insomnia with a total of 1 265 015 participants (718 828 female). All papers in the analysis were epidemiological studies of the general population reporting on sex-specific prevalence figures in adults. In order to identify and properly account for heterogeneity between studies, statistics were used to test the homogeneity of the specific set of effect sizes and the significance of moderators. To prevent any bias, large samples were analyzed separately from small samples. In order to investigate the genuine sex difference in the risk of insomnia, the analysis focused on quality studies that were “large...with structured or semi-structured diagnostic interviews and based on stringent operational criteria”.

To investigate the frequency effect, studies were divided into three groups (any frequency, frequent or always, and severe), and prevalence was divided between current and long-term insomnia studies. Studies that explored insomnia

subtypes were analyzed separately. Time trends were also analyzed (studies before and after 1990).

The results showed a risk ratio of 1.41 (95% confidence interval 1.28–1.55) for women versus men. The trend of higher female prevalence was consistent and progressive with age, and greater relative differences were seen in the elderly. The female prevalence in the meta-analysis of large and quality studies was higher than that of small and non-quality studies. In addition, a female preponderance of insomnia was found among different criteria, frequencies, and duration, suggesting the possibility of cross-cultural differences in the sex risk of insomnia. Although there is an obvious female prevalence among different regions, there was a relatively lower female preponderance in East Asia. The prevalence of insomnia in earlier studies was much higher than that in recent studies, possibly due to the more stringent diagnostic criteria of insomnia used after 1990. This suggests that the criteria of recent studies were more rigorous and the estimation of the prevalence rate was more reliable. However, no significant time trend was seen in this study. In conclusion, these data confirm the female predisposition in the risk of insomnia.

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## POSITIVE AIRWAY PRESSURE THERAPY

### Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea

Marcus CL, Rosen G, Ward SL et al.  
*Pediatrics* 2006;**117**:e442–51.

The objectives of this prospective, multicenter study conducted on 29 children (aged 2–16 years) with obstructive sleep apnea (OSA) were three-fold: to assess the efficacy of and adherence to positive airway pressure therapy (PAP) in treating OSA and to evaluate, in a double-blind manner, the differences that may exist between continuous PAP and bilevel PAP in the therapy of OSA. As expected, both modalities of PAP were highly successful in treating pediatric OSA, as evaluated via polysomnography. Compliance to, and prolonged adherence to PAP was, in general, suboptimal, thereby limiting its efficacy. No significant disparities were observed between the two modes of pressure.

Upper airway obstruction in children with obstructive sleep apnea (OSA) syndrome is most often a consequence of

adenotonsillar enlargement but other factors, such as obesity, craniofacial structure, and abnormal upper airway tone, may predispose to the condition necessitating interventions besides an adenotonsillectomy. In these scenarios, positive airway pressure (PAP) is often used as an alternative, efficacious therapy for OSA. The present study aimed to objectively assess both efficacy and compliance to PAP treatment using polysomnography (PSG) and a computerized usage meter, respectively. Concurrently, it aimed to evaluate, in a double-blind manner, the same two parameters with respect to continuous PAP (CPAP) and bilevel PAP (BPAP).

The participants in this prospective, multicenter study were children aged 2–16 years who had objective and subjective criteria of OSA, and who were either ineligible for or had undergone unsuccessful surgical interventions, specifically adenotonsillectomy. Patients underwent a baseline and PAP titration PSG followed 6 months later by a second PSG while receiving PAP therapy. Adherence was objectively measured via a computerized usage meter, and changes in vitals, weight, and height were recorded; subjective assessments were also solicited from the children's parents.

Formal behavioral interventions and assistance, including a period of habituation prior to PAP titration and intensive clinical support while on the device, were instituted in order to achieve successful implementation of PAP. Sixteen patients were randomly assigned to BPAP and thirteen to CPAP. Ultimately, 19 patients completed the proposed protocol for the study. A mean nightly utilization of <3 h/night constituted non-adherence to PAP, and there were no significant differences in factors such as age, gender, and race between those who were compliant or non-compliant. Furthermore, no significant differences in use were detected between those utilizing CPAP or BPAP, with mean nightly use for those with downloadable data being 5.3 h/night. Mean nightly use was 3.8 h/night for the total 29 patients when accounting for the loss in follow-up. After treatment with PAP for 6 months, there were significant improvements in all respiratory parameters when objectively evaluated with PSG, specifically in the apnea-hypopnea index (AHI) and in arterial oxygen saturation, with AHI ranging 0–17 events/h, a decrease from the baseline range of 3–115 events/h. Subjective assessments provided by the participants' parents noted significant improvements in snoring, nocturnal breathing difficulties, and sleepiness. In contrast, no changes in growth parameters (either height or weight) or blood pressure were observed after 6 months of PAP. Side-effects that limited PAP usage included problems with the equipment (14%) and mask (21%) in the acute period, and, after 5 months of usage, a 10% dissatisfaction with either.

The limitations of the study, as proposed by the researchers, include the low retention rate of participants,

which reflects non-adherence to PAP therapy itself. In addition, although the CPAP and BPAP modalities were themselves assessed in a double-blind manner, there was not a control group for the PAP therapy. Nevertheless, despite these minor limitations, a convincing argument can be made for use of PAP therapy in the pediatric and adolescent population for improving respiratory parameters during sleep, while simultaneously acknowledging behavioral and technical limitations that may curtail its use and, hence, its efficacy.

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### Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure

Norman D, Loredi JS, Nelesen RA et al.  
*Hypertension* 2006;**47**:840–5.

While it is well established that obstructive sleep apnea (OSA) is associated with hypertension, there is only modest evidence to suggest that the treatment of this condition with continuous positive airway pressure (CPAP) or oxygen reduces blood pressure. The effects of CPAP, sham-CPAP, and oxygen on blood pressure were studied in 46 OSA patients. The results demonstrated that CPAP improves daytime and night-time mean and diastolic blood pressure, and systolic pressure at night-time only, while supplemental oxygen had no effect on blood pressure.

It is well established that patients with obstructive sleep apnea (OSA) are at increased risk for daytime hypertension. Considering the strength of this relationship, it is surprising that studies of continuous positive airway pressure (CPAP) as an effective therapy for OSA have shown inconsistent effects on blood pressure reduction. This randomized, double-blind, sham-CPAP controlled study by Norman and co-workers employed continuous ambulatory blood pressure monitoring to examine whether 2 weeks of effective CPAP therapy might improve hypertension in 46 OSA patients. The authors also included a comparison with supplemental oxygen to determine whether preventing nocturnal hypoxemia, which has been theorized to be the mechanism of hypertension in OSA, might improve blood pressure.

The authors found that CPAP therapy led to a significant improvement in mean and diastolic blood pressure during both the night and day compared with sham-CPAP. However, systolic blood pressure improved only during the night-time. There was no evidence that supplemental oxygen had any therapeutic effect on blood pressure, which argues against

hypoxemia as an important mechanism of hypertension in OSA patients.

These findings suggest that CPAP treatment of OSA patients improves mean and diastolic blood pressure, but does not address the elevation in systolic blood pressure experienced by many individuals with OSA. A possibility that should be considered is whether the physiological changes that mediate the systolic hypertension might be more persistent or irreversible. In this regard, it will be interesting to determine if it is possible to prevent the development of systolic hypertension with CPAP therapy (even though once established it may not resolve with CPAP treatment). Similarly, while the findings suggest that oxygen therapy does not reduce hypertension in OSA patients, it may prevent the development of hypertension. These findings undermine the centrality of hypoxemia as a mechanism of hypertension in OSA and highlight the need to explore the importance of other mechanisms including recurrent changes in intra-thoracic pressure, the effects of sleep disturbance, and the changes in autonomic system function that often occur with OSA events.

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### Effect of continuous positive airway pressure on soluble CD40 ligand in patients with obstructive sleep apnea syndrome

Kobayashi K, Nishimura Y, Shimada T et al.  
*Chest* 2006;**129**:632–7.

This study examined whether CD40 ligation contributes to outcomes in patients with obstructive sleep apnea (OSA) syndrome. The results of this study suggest that the soluble CD40 ligand is a key factor linking OSA and atherosclerotic progression.

The association of obstructive sleep apnea (OSA) with vascular morbidity, including hypertension, coronary artery diseases, and stroke, is of a major concern. Since OSA may independently contribute to these vascular diseases, it is important to understand the pathogenetic mechanisms of atherosclerosis caused by OSA. The present study evaluated the relationship between soluble CD40 ligand (sCD40L) levels and outcomes in patients with OSA, and whether treatment with nasal continuous positive airway pressure (nCPAP) decreased plasma levels of sCD40L.

A total of 35 patients with an apnea–hypopnea index (AHI)  $\geq 30$  (aged  $51 \pm 13$  years; five female) and 16 controls with an AHI  $< 5$  (aged  $41 \pm 13$  years; three female) were

studied. Serum levels of sCD40L, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and hypersensitive C-reactive protein (hsCRP) were measured before and after nCPAP therapy for 3 months. OSA patients retired to bed at 21:00, and peripheral venous blood samples were collected at the moment of waking. Blood samples were also collected from patients with severe OSA during the morning as well as 1 night, 1 month, and 3 months after nCPAP therapy. All patients completed a polysomnography recording after screening with an "apnomonitor".

Levels of sCD40L were significantly higher in patients with severe OSA than in controls ( $p < 0.01$ ) and levels of serum TNF- $\alpha$  were also significantly higher in those with OSA compared with controls ( $p < 0.01$ ); hsCRP levels did not significantly differ between the groups. Before nCPAP therapy there was a positive correlation between sCD40L and TNF- $\alpha$  levels in OSA patients ( $p = 0.02$ ), but not hsCRP, ( $p > 0.05$ ). Patients with severe OSA did not receive any other medications for the risk of atherosclerosis while undergoing the 3-month nCPAP treatment, and no new cardiovascular diseases developed in this group. Significant improvements were also seen in the AHI after treatment with nCPAP ( $p < 0.0001$ ). Serum sCD40L levels that significantly decreased as soon as 1 night after nCPAP therapy in patients with OSA were maintained for 3 months. Therapy with nCPAP similarly reduced TNF- $\alpha$  levels during the first 3 months of treatment, but no effect was seen on hsCRP.

Higher serum levels of sCD40L and TNF- $\alpha$  were shown in OSA patients compared with controls, and treatment with nCPAP for 3 months improved these levels in OSA patients.

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### Equivalence of auto-adjusted and constant continuous positive airway pressure in home treatment of sleep apnea

Nussbaumer Y, Bloch K, Genser T et al.  
*Chest* 2006;**129**:638–43.

This study was designed to compare the efficacy of sleep apnea home therapy with either computerized auto-adjusted or constant continuous positive airway pressure in obstructive sleep apnea syndrome.

Obstructive sleep apnea (OSA) syndrome affects 2–4% of adults and is associated with a negative impact on quality of life and excessive daytime sleepiness. Continuous positive airway pressure (CPAP) has been shown to improve

vigilance and quality of life. As CPAP requirements vary, there has been considerable interest in devices that can adjust mask pressure using feedback control during treatment from pressure, flow, or other signals. Allowing treatment pressure to adjust automatically would mean a decrease in CPAP when apneas and hypopneas disappear, and an increase when they reappear. Therefore, continual adaptation of the CPAP mask pressure to reflect the actual needs of the patient might improve the therapy's efficacy through prevention of high pressures in the mask.

A total of 30 patients with excessive sleepiness and apnea-hypopnea index (AHI)  $> 10$  obstructive events participated in this study (mean age 49 years; three female). A randomized, double-blind, controlled, cross-over trial was performed comparing the efficacy of sleep apnea home therapy using a novel CPAP machine operated in either auto-adjusted (aCPAP) or constant (cCPAP) mode. Patients were randomly assigned to 1 month of home therapy with either aCPAP or cCPAP, followed by 1 month of the alternative treatment. Mean Epworth Sleepiness Scale (ESS) scores, sleep resistance time, and AHI were evaluated at baseline and after 1 month of treatment.

At baseline, ESS scores were  $12.7 \pm 0.6$ , mean sleep resistance time was  $26 \pm 2$  min, and mean AHI was  $41.1 \pm 3.6/h$ . After 1 month of treatment with aCPAP, mean ESS score, sleep resistance time, and AHI were significantly improved ( $6.5 \pm 0.6$ ,  $37 \pm 1$  min, and  $4.6 \pm 0.7/h$ , respectively; all  $p < 0.05$  versus baseline). This was similar to the results achieved with cCPAP.

Twenty-six patients preferred aCPAP ( $p < 0.001$ ). The sleep questionnaire indicated that there were significant differences in noise perception and discomfort from high pressure in favor of aCPAP. No differences in sleep quality or side effects were noted. There were no differences between the two treatments in daytime sleepiness, impaired quality of life, and nocturnal respiratory disturbances, and in both treatments a significant and clinically relevant relief of the OSA symptoms was achieved. These results suggest that the aCPAP device performs well in respiratory event detection and automatic mask pressure adjustment, and that this was appreciated by the patients who indicated a clear preference for the aCPAP.

In conclusion, although aCPAP and cCPAP showed no significant differences with regard to major outcome parameters such as objective sleepiness, symptoms, or quality of life, the majority of patients preferred aCPAP treatment over cCPAP in the initial phase of therapy. Since aCPAP does not require initial titration, it may be a simple and promising modality for sleep apnea home therapy.

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## RESTLESS LEGS SYNDROME

### VIM deep brain stimulation does not improve pre-existing restless legs syndrome in patients with essential tremor

Ondo W.

*Parkinsonism Relat Disord* 2006;**12**:113–4.

This succinct article presents a study conducted on nine patients with severe essential tremor (ET) who were unresponsive to pharmacological interventions and who had pre-existing restless legs syndrome (RLS). The study assessed the efficacy of deep brain stimulation (DBS) in ameliorating these two conditions. Results revealed an improvement in patients' ETs with DBS, but not in those with RLS.

Although restless legs syndrome (RLS) has recently gained a more significant vantage point and greater scrutiny by sleep specialists, its etiology remains elusive. For example, although it is known that the syndrome affects approximately 10% of Caucasians and harbors a genetic predisposition, it is also an indicator of other factors, such as iron depletion, pregnancy, neuropathy, and renal failure. It has been postulated that a dopaminergic mechanism is at work in this condition since, in general, dopamine supplementation effectively relieves RLS symptoms. Despite this rational theorization, the precise anatomical locale and pathophysiology of RLS remains unrecognized. In contrast, essential tremor (ET), which is considered to be the most common movement disorder as it affects approximately 1–2% of the population, has been satisfactorily localized to a dysfunction at the ventralis intermedius nucleus (VIM). In the study author's view, a significant portion of those with ET also harbors the subjective symptoms inherent to RLS.

The author undertook a study to assess whether deep brain stimulation (DBS) to the VIM – the pathological site of ET – would also ameliorate RLS symptoms in subjects who presented with both conditions. The nine patients studied had severe ET and had failed pharmacological interventions, while also harboring RLS of varying degrees of severity. Subsequent to DBS, none of the patients reported improvements in subjective symptomatology of RLS but noticed a fair-to-excellent improvement of their ETs. Based on the above findings, the author concludes that the thalamic VIM is not the pathological site for the emergent symptoms of RLS, and postulates a possible role of the globus pallidus, based on the relative increased prevalence of RLS in Parkinson's disease patients.

Although the theoretical basis for the present study is both provocative and innovative, there are several shortcomings that should be considered. Firstly, although some inferences

may be made from this study, it is obvious that the number of patients is too small to support any conclusive statements. Secondly, it is uncertain from this study whether the nine patients had clearly "idiopathic" RLS, with five harboring a family history, two with documented neuropathy, and one with a low serum ferritin. It could be postulated that VIM DBS may have had an effect, however insignificant, if the criteria for RLS had been more stringent. Thirdly, it is not mentioned whether any of these patients were diagnosed with, or at least had symptoms of, Parkinson's disease; as the author suggests, this could indicate a different pathological basis for the RLS. Lastly, the prospective analysis of the study is undefined, as a delineated timeline for follow-up after the DBS is not mentioned.

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### Evaluation of periodic leg movements and associated transcranial magnetic stimulation parameters in restless legs syndrome

Kutukcu Y, Dogruer R, Yetkin Set al.

*Muscle Nerve* 2006;**33**:133–7.

Transcranial magnetic stimulation (TMS) was used to determine whether a difference in motor threshold and cortical silent period (CSP) was found between 20 primary restless legs syndrome (RLS) patients and 15 age- and gender-matched controls. The CSP was shortened in RLS patients and improved significantly with RLS treatment, but was unrelated to periodic leg movement index. This finding, while non-specific, suggests an alteration in cortical dynamics in RLS patients.

In order to better understand the role of motor cortex neuronal circuits in restless legs syndrome (RLS), these investigators studied the motor threshold for transcranial magnetic stimulation (TMS) and the cortical silent period (CSP) that follows in 20 patients with primary RLS, before and after 1 month of uncontrolled treatment (eight received levodopa, eight received cabergoline, and two were treated with ropinirole – no dosages were provided). The findings were compared with 15 age- and gender-matched controls. While there were no differences in motor threshold, the CSP was significantly shorter in the RLS patients than in the controls (mean of approximately 100 ms vs. 125 ms) and increased to a mean of approximately 115 ms with treatment.

The relatively shortened CSP in RLS patients has previously been reported and is of interest with respect to cortical mechanisms in RLS. While the authors place importance on the lack of a relationship between the CSP and periodic leg

movement (PLM) index (a correlate of sleep efficiency in RLS patients), the relevance of this is unclear. It may be that the CSP is specifically related to the RLS and not the PLMs that are often associated with this syndrome. In this regard, it would have been helpful if the study authors had indicated whether there was an association between CSP and improvement in RLS symptoms, as reported by the study subjects.

In terms of mechanistic implications, the authors suggest that the shorter CSP in RLS patients indicates a hypoactivity of inhibitory interneurons in the motor cortex. While provocative, this suggestion is hard to associate with the observed RLS symptomatology. The period of inhibition normally lasts approximately 125 ms and is shortened to 100 ms in RLS patients. It is difficult to understand how this 25 ms difference might relate to the spontaneous urge to move, which is the hallmark of RLS and is completely absent in control patients. While the 25 ms difference may underlie a difference in cortical dynamics that result in symptoms of RLS, at face value one might expect individuals with RLS to differ to a greater extent from those without. For example, patients without RLS would experience the urge to move but would be delayed in the degree to which their movement would satisfy this urge compared with RLS patients. Clearly, this interesting and clinically important finding requires further study.

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### **Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial**

Bogan RK, Fry JM, Schmidt MH et al.  
*Mayo Clinic Proc* 2006;**81**:17–27.

Ropinirole, a dopamine agonist, has been the subject of several large-scale clinical trials investigating its efficacy in the treatment of restless legs syndrome (RLS), for which it was recently approved by the US Food and Drug Administration. This 12-week flexible-dose placebo-controlled trial of ropinirole is the largest ropinirole RLS study to date and, consistent with prior studies, demonstrated efficacy in sleep and function ratings, with the most common adverse effects being nausea, vomiting, and somnolence.

Restless legs syndrome (RLS) affects an estimated 5–10% of the adult population; however, until recently there were no agents approved by the US Food and Drug Administration (FDA) for the treatment of this common condition. In recent years, the non-ergot dopamine agonist ropinirole has been the subject of a number of large-scale clinical trials that have

demonstrated its safety and efficacy in the treatment of RLS, leading to US FDA approval of the agent for RLS therapy.

This 12-week, parallel group, flexible-dose, placebo-controlled study of ropinirole by Bogan and co-workers represents the largest RLS trial published to date and involved 381 RLS patients. Flexible dosing was started at 0.25 mg/day and could be increased up to a maximum of 4 mg/day over the course of the study to achieve the optimal effective and tolerated dose, based on the clinical judgment of the investigators. As such, this study provides a better indication of the likely efficacy and safety that would be observed in clinical practice rather than in a traditional fixed-dosing study.

Consistent with prior studies, evidence of sustained efficacy over the trial period in terms of the primary outcome measure was determined using the International Restless Legs Scale (IRLS), in addition to a number of self-ratings of sleep and daytime function. Also, in agreement with prior work, the most common adverse effects were nausea (ropinirole 42.8% vs. placebo 7.8%), vomiting (ropinirole 8.6% vs. placebo 1.6%), and somnolence (ropinirole 12.8% vs. placebo 6.7%).

Together with other ropinirole studies, these data form the most important existing set of studies of RLS treatment. Given the prevalence and clinical impact of RLS, it is anticipated that this body of work will be followed by other efforts to develop and empirically characterize much needed RLS therapies.

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## POLYSOMNOGRAPHY

### **Cost-effectiveness of split-night polysomnography and home studies in the evaluation of obstructive sleep apnea syndrome**

Deutsch PA, Simmons MS, Wallace JM.  
*J Clin Sleep Med* 2006;**2**:145–53.

This report used a decision-tree model to assess both the cost-effectiveness and quality-adjusted life years associated with various modes of sleep studies utilized to diagnose obstructive sleep apnea syndrome, and highlighted the complexities inherent in such comparisons. Although they conclude that no significant differences in cost or efficacy exist between a full-night polysomnogram (PSG) and split-night PSG alternatives, they also suggest that home studies may be a viable alternative if economic and other constraints co-exist.

Given the sustained proliferation of sleep laboratories in the Western hemisphere and the varied studies available for

diagnosing obstructive sleep apnea (OSA) syndrome via these modalities, the present article is both timely and necessary. Although the aims of this study are modest, namely to assess the cost-effectiveness and quality-adjusted life years (QALYs) associated with three modes of sleep studies, the far-reaching effects and implications of such aims are significant for assessing the utilization of societal resources at large.

The authors targeted a cohort of people, aged 30–64 years, (85% male), whose symptoms were suggestive of OSA. This group underwent one of three studies:

- A full-night polysomnogram (PSG), which comprised of an initial diagnostic PSG and continuous positive airway pressure (CPAP) titration during two overnight stays.
- A split-night PSG, in which a diagnostic portion was undertaken 2 h prior to a CPAP titration.
- Unattended home partial sleep monitoring with a subsequent home CPAP titration utilizing an autotitrating device.

An analytical timeline of 5 years was used to assess the cost-utilization and health benefits associated with the three modes of diagnosis. A decision-tree model was utilized to formulate the data, which was then calculated via a probabilistic approach rather than in a case-based manner. As expected, both cost and QALYs were greatest for the full-night PSG and lowest for the home studies. In addition, the home studies had a greater number of dropouts and lower rates of CPAP acceptance, which ultimately progressed to an evolution of patients with untreated OSAS. However, surprisingly, no significant differences were appreciated in cost or efficacy when comparing the full-night and split-night PSGs, the former garnering only an additional 7 quality-adjusted days of survival, or 0.02 QALYs. Ultimately, the cost-efficacy of the three studies rests on the willingness to pay, which, when restricted to low amounts, favors the home-studies pathway and, when higher, favors the other modalities.

The authors acknowledge the limitations of the study, including a restriction of the study options that were analyzed as a pathway (i.e. a full-night PSG followed by a home CPAP autotitration rather than a laboratory titration was not assessed), which could have potentially altered the conclusions. Secondly, other treatment modalities for OSA therapy, such as oral appliances and surgical procedures, were not mentioned in the study. Lastly, economic costs were calculated from the perspective of a third-party payer, such as Medicare, rather than from the purview of society in general. Irrespective of these limitations, the study suggests that full-night and split-night PSGs are similar in efficacy and cost, and other variables such as availability of

space and resources need to be addressed for a treatment choice to be made.

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### Polysomnographic characteristics in normal preschool and early school-aged children

Montgomery-Downs H, O'Brien L, Gulliver T et al. *Pediatrics* 2006;**117**:741–53.

In order to investigate overnight polysomnography (PSG) measures in normal children aged 3–7 years, a retrospective analysis of PSG evaluations were conducted in two large community-based studies. Participants included 542 healthy children. Since the greatest differences in PSG occur between 5 and 6 years of age, analyses were performed for children aged 3–5 and  $\geq 6$  years. The findings of the current study are, to date, the largest compilation of normative reference values for laboratory-based pediatric PSG.

As a result of the increasing data indicating a high prevalence of sleep disorders among children and the accompanying health risks, interest in pediatric sleep disorders continues to grow. The potential somatic and biobehavioral effects associated with pediatric sleep disorders make it important to identify normative values for children from an early age to ensure accurate diagnosis.

Participants included 153 children aged 3–5 years old (45% female) and 388 children aged 6–7 years (48.5% female). Retrospective data were obtained from children attending either preschool or first-grade classes who had been participants in two ongoing large-scale community studies. Screening questionnaires were sent home to evaluate children for evidence of sleep-disordered breathing (SDB). Control children who did not have a risk of SDB were recruited into both studies and were included in the present analysis. Participants in the original studies were excluded if they had documented snoring during polysomnography (PSG), an obstructive apnea-hypopnea index (AHI) of  $\geq 1$ , or a periodic leg movement index of  $\geq 5$ . The standard overnight PSG evaluation was performed at the Sleep Medicine Center at Kosair Children's Hospital (University of Louisville, KY, USA).

A wide array of sleep parameters was investigated in both age groups. The rapid-eye movement period was brief to start and lengthened during the night in both age groups, showing sleep to be cyclical. However, the sleep cycle was distinct between the age groups, with only the older group having a decrease in cycle length across the night. Average obstructive apnea indices were 0.03/h of total sleep time (TST) for the younger age group, and 0.05/h of TST for the older children.



Central apnea indices were 0.82/h and 0.45/h of TST for the children aged 3–5 and 6–7 years, respectively. AHI differed according to body position and older children spent a greater amount of time supine. A total of 20% of subjects had end tidal CO<sub>2</sub> values of >45 mmHg, and 2.2% had recorded values of >50 mmHg during ≥50% of TST. Gender-by-age-group differences on several measures were significant; specifically, younger females had higher sleep efficiency (p=0.03), less wake (p=0.02), and more stage 3 sleep (p=0.007). There was a large variability seen in all measures.

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## MISCELLANEOUS

### The relationship between depression and sleep disturbances

Kaneita Y, Ohida T, Uchiyama M et al.

*J Clin Psychiatry* 2006;**67**:196–203.

This study examines the relationship between depression and both sleep duration and subjective sleep sufficiency in the general population. Self-administered questionnaires were gathered from 24 686 individuals throughout Japan. Answers revealed that sleep duration had a U-shaped association, and subjective sleep sufficiency had an inverse proportional relationship, with symptoms of depression.

Research has shown that depression and sleep disturbances are closely related. Sleep disturbances may affect depression, and treatment of depression has been shown to significantly improve sleep. Several studies also suggest that sleep disturbances are risk factors for the later development of depression. It is therefore of great importance to clarify the relationship between these two conditions to help in their prevention and effective management.

A survey was conducted among the general population in 300 communities throughout Japan. Investigators distributed questionnaires to each household and collected them a few days later. Data was obtained on 24 686 individuals aged ≥20 years; sleep status, including sleep duration, subjective sleep sufficiency, and the presence or absence of insomnia symptoms were evaluated. The Center for Epidemiologic Studies-Depression Scale (CES-D) was used to assess for the presence of depression. Although this scale was designed for screening and not for diagnosis of depression, a score of ≥16 is generally accepted as highly suggestive of depression and a score of ≥25 has been used for more severe depression in several studies.

The results showed that individuals with a sleep duration of <6 h or >8 h tended to be more depressed than those whose sleep duration was 6–8 h. The prevalence of depressive symptoms and mean CES-D scores were significantly higher among women than men (p<0.01), and scores of ≥16 or ≥25 were significantly greater for individuals with symptoms of insomnia than for those without. A multidirectional logistic regression analysis also revealed a unidirectional association between lower subjective sleep sufficiency and worse symptoms of depression.

The results showed that sleep duration exhibited a different association than subjective sleep sufficiency with symptoms of depression. This suggests that these two sleep parameters each have their own impact with regard to depressive symptoms.

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### Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent

Wyatt JK, Dijk DJ, Ritz-de Cecco A et al.

*Sleep* 2006;**29**:609–18.

This double-blind, placebo-controlled study involving 36 young, healthy participants assessed the effects of exogenous melatonin, either in a physiological or pharmacological dose, on both sleep latency and efficiency in sleep episodes spanning a full array of circadian phases. In the absence of endogenous melatonin, the two exogenous doses significantly increased sleep efficiency compared with placebo, but failed to replicate such findings in its presence. Furthermore, exogenous melatonin did not significantly affect sleep latency, core body temperature, or percentages of sleep stages.

The history of melatonin use is controversial, spanning a range of reported outcomes with regard to its efficacy in altering circadian phases and its role as a hypnotic. This debate continues as melatonin has again come to the forefront with the emergence of the recent US Food and Drug Administration-approved medication, ramelteon, and its purported efficacy as a hypnotic. The researchers of this study, although acknowledging the potential phase-shifting effects of melatonin, have focused on its role as a hypnotic when administered exogenously across a wide array of circadian phases. Previous trials have shown that although the administration of exogenous melatonin prior to normal nocturnal episodes of sleep did not alter sleep latency or total sleep time, its administration prior to daytime nap episodes affected both of those parameters. The authors of

the present article aimed to elaborate on those findings by administering melatonin across a range of circadian phases and regulating the homeostatic mechanisms prior to nap times; this had not been considered in previous trials.

The 36 participants in the present study, aged 18–30 years, were healthy men and women who received either 0.3 mg or 5.0 mg of oral melatonin or a placebo equivalent 30 min prior to a 6.67-h sleep episode during a 27-day forced desynchronous paradigm. Rest/activity cycles, consisting of 13 h 20 min awake and 6 h 40 min sleep episodes were strictly enforced with incremental 4 h shifts, deemed to be outside the “range of entrainment of the circadian pacemaker”, as designated by the authors. The participants were also studied in windowless suites with dim light to avoid both the light-inducing suppression of endogenous melatonin as well its alteration of circadian rhythmicity. Objective measurements of latency to sleep and sleep consolidation were confirmed via an abbreviated form of polysomnogram. Plasma melatonin levels were also measured during all forced desynchronized segments of the protocol.

As has been previously reported, this study confirmed that melatonin administration affects sleep efficiency only during the circadian day, at times when the circadian system enforces wakefulness. Its administration during the circadian night did not affect sleep efficiency. Interestingly, when endogenous melatonin was absent (i.e. the circadian day), the administration of exogenous melatonin was less efficacious than for phases when endogenous melatonin was present (i.e. the circadian night). However, no other parameters of sleep such as sleep onset latency, core body temperature, or sleep staging were affected by either doses of the exogenous melatonin.

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### **Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy**

Merlino G, Piani A, Dolso P et al.

*Nephrol Dial Transplant* 2006;**21**:184–90.

The prevalence of sleep disorders in patients undergoing dialysis due to end-stage renal disease was assessed in a large population of patients recruited from 20 dialysis centers in Italy. Results obtained via a self-administered questionnaires revealed at least one sleep disorder in 80% of these patients. Insomnia and obstructive sleep apnea constituted the majority of the disorders, although there was also a high prevalence of restless legs syndrome and excessive daytime somnolence.

Although it is recognized that patients undergoing dialysis secondary to end-stage renal disease have a variety of sleep disorders, it has been difficult to precisely categorize and quantify these due to small sample sizes, and questionnaires that were not powered to identify specific sleep disturbances. The present study undertook the task of assessing both previously recognized and unrecognized sleep disorders (in addition to factors that may have predisposed or exacerbated them) among 883 patients undergoing dialysis for  $\geq 6$  months selected from 20 dialysis centers in north-eastern Italy. Responses were obtained via a two-part questionnaire, completed by both the nephrologists and the patients, with specific criteria established to assess for the various sleep disturbances.

Results of the study revealed there to be at least one sleep disorder in 708 (80.2%) patients that was not related to sex, weight, body mass index, caffeine intake, or drug use. However, there was a statistically significant correlation with age, daily ethanol use, cigarette smoking, diabetes, polyneuropathy, and dialysis shift in the morning. Insomnia appeared to be the most common sleep disturbance, occurring in 69.1% of the participants, with a predominance of the sleep maintenance component. There is a high risk for sleep apnea in these patients, and based on the Berlin Questionnaire, 136 patients (23.6%) were included in this category. Apnea was strongly associated with excessive daytime somnolence, which itself comprised 11.8% of the total sample. According to the criteria set forth by The International Restless Legs Syndrome (RLS) Study Group, 152 patients (18.4%) were given a diagnosis of RLS, even when accounting for the possibility of a dopamine agonist causing the insomnia. Other sleep disorders that were considered by the questionnaires included nightmares (13.3%), possible rapid eye movement-behavior disorder (2.3%), sleepwalking (2.1%), and possible narcolepsy (1.4%).

Certain limitations of this study should be addressed, including the use of a questionnaire without polysomnographic confirmation of the reported sleep disorder, for example for obstructive sleep apnea or narcolepsy, which, as the authors acknowledge, is higher than reported in the general population. Metabolic factors were unaccounted for when a diagnosis of RLS was given; thus, it was not possible to differentiate idiopathic RLS from its secondary form arising from the dialysis itself. Despite these limitations, this study will help to pave the way for future research into the complexity of sleep disturbances in those with end-stage renal disease undergoing dialysis.

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# 159th Annual Meeting of the American Psychiatric Association (APA)

Toronto, ON, Canada, May 20–25, 2006

Paul Ballas and Karl Doghramji

Thomas Jefferson University Hospital, Philadelphia, PA, USA

The 159th Annual Meeting of the American Psychiatric Association (APA) was held May 20–25, 2006 in Toronto, ON, Canada. A substantial amount of new research on sleep and sleep disorders was presented at the conference, reflecting the importance of this aspect of health in the psychiatric community. Information was presented that advanced our basic understanding of the mechanics and need for sleep, as well as important developments in the treatment of specific sleep disorders, including sleep deprivation, parasomnias, and primary and secondary insomnia. This report details a selection of key presentations from this conference.

## Efficacy of armodafinil

Armodafinil is the R-enantiomer of racemic modafinil, an alertness-promoting agent. Russell Rosenberg (Northside Hospital Sleep Medicine Institute, Atlanta, GA, USA) presented evidence from a study of armodafinil aimed at reducing symptoms of fatigue. Patients (n=150) with narcolepsy who were experiencing excessive sleepiness were evaluated in this 12-week, placebo-controlled, multicenter study. Subjects received armodafinil at either 250 mg/day (n=67) or 150 mg/day (n=65), or placebo (n=64). Subjective evaluation of the severity of fatigue and its impact on functioning was assessed using the nine-item Brief Fatigue Inventory (BFI), which includes six interference items: relations with others, enjoyment of life, normal work, walking ability, mood, and general activity. Patients were assessed as having moderate-to-severe fatigue at baseline. Patients in both armodafinil groups had significantly reduced fatigue scores at the last follow-up visit compared with the placebo group (mean changes from baseline±SD  $-1.5\pm 2.1$ ,  $-1.3\pm 2.1$ , and  $-0.3\pm 1.9$  in the armodafinil 150 mg/day, armodafinil 250 mg/day, and placebo groups, respectively;  $p<0.05$ ) and had significantly improved scores in all six interference items ( $p<0.05$ ). This study offered evidence that armodafinil may reduce the severity and impact of fatigue on daily living in patients with narcolepsy.

Keith Wesnes (Cognitive Drug Research Ltd., Goring-on-Thames, UK), Gwendolyn Niebler (Cephalon, Inc., Frazer, PA, USA), and Sanjay Arora (Pacific Sleep Medicine Services,

San Diego, CA, USA) presented research on the effects of armodafinil on attention in subjects with shift work sleep disorder (SWSD), narcolepsy, and obstructive sleep apnea/hypopnea syndrome (OSA/HS). A total of 1108 subjects participated in four double-blind, 12-week trials of the medication. Subjects received placebo or armodafinil (150 or 250 mg/day) and the Cognitive Drug Research computerized assessment system was used to assess attention at 4, 8, and 12 weeks. Results revealed that armodafinil improved the continuity of attention in patients with SWSD at the final study visit compared with those receiving placebo. Cognitive reaction time was also improved in patients with narcolepsy in the armodafinil groups. This data suggests that armodafinil can improve attention in patients with excessive sleepiness due to SWSD or narcolepsy.

Milton Erman, Sanjay Arora (Pacific Sleep Medicine Services, San Diego, CA, USA), and Gwendolyn Niebler (Cephalon, Inc., Frazer, PA, USA) presented data from the same trial indicating that armodafinil may be beneficial in treating the excessive sleepiness that can be a consequence of many sleep disorders. Measures utilized included the Clinical Global Impression of Change, Maintenance of Wakefulness Test (MWT) in the OSA/HS and narcolepsy studies, and the Multiple Sleep Latency Test (MSLT) in SWSD. The results revealed that, compared with placebo, armodafinil improved overall clinical conditions, and specifically improved sleep latencies in subjects with SWSD, OSA/HS, or narcolepsy. The most common adverse event reported during the trial was headache. This data suggests that armodafinil is beneficial for improving the general clinical condition and excessive sleepiness of patients with SWSD, narcolepsy, and OSA/HS.

## Insomnia

A symposium entitled “Insomnia – what is it?” was held in order to educate participants on the presentation and treatment of primary and secondary insomnia. New data on the epidemiology, prevalence, and phenomenology of insomnia were proffered. A review of the role of cytokines in

sleep and practical guidelines for the treatment of insomnia were also presented.

Edward Bixler (Penn State College of Medicine, Hershey, PA, USA) presented a talk on the epidemiology of chronic insomnia. Insomnia is the most prevalent sleep disorder, affecting approximately one-third of the adult population, with 10% of these requiring medical attention. A study of the general population in central Pennsylvania revealed that insomnia was strongly associated with depression, female gender, and socioeconomic status, and weakly associated with anemia, hypertension, and colitis. Primary sleep disorders were not closely associated with insomnia. These findings suggest that mental health is strongly associated with insomnia and psychiatrists may play an important role in its evaluation and treatment.

Alexandros Vgontzas (Penn State College of Medicine) gave a presentation on the clinical implications of biological models of chronic insomnia. Specifically, he addressed three questions regarding the understanding of insomnia:

- Is sleep loss a consequence or cause of insomnia?
- Does insomnia cause symptoms throughout a 24-h period or only have an affect on sleep at night time?
- What is the relationship between insomnia and depression?

Dr Vgontzas and colleagues asserted that insomnia was not an affliction of sleep loss but a disorder of physiological and emotional hyperarousal with symptoms that persist throughout the 24-h cycle. The speakers also presented findings revealing that the neurobiology of depression-associated insomnia differs from that of depression with a secondary complaint of sleep loss.

### Sleep and medical illness

The symposium "Sleep, fatigue, and depression in medically ill patients" explored the interaction between sleep and fatigue in various medical illnesses, including breast cancer, diabetes mellitus, and renal transplantation. Sonia Ancoli-Israel (University of California San Diego, CA, USA) presented data on the effects of chemotherapy for breast cancer on fatigue and sleep. Eighty-five women newly diagnosed with breast cancer were assessed before and after chemotherapy. The study used actigraphy to measure exposure and sleep, and questionnaires to assess depression, fatigue, sleep, and functional outcomes. Findings revealed that prior to chemotherapy the women slept for approximately 6 h/night and napped for >1 h. The data also revealed that changes in sleep and light exposure were correlated, but not causally related, to the fatigued experience during chemotherapy. This suggests that prior to chemotherapy for breast cancer, patients had disturbed sleep

and experienced fatigue, both of which worsened after initiating treatment.

Wayne Katon (University of Washington Medical Center, Seattle, WA, USA) presented data on the impact of sleep and fatigue in patients with diabetes mellitus. A total of 4800 subjects with diabetes mellitus were assessed for symptom burden, adherence to self-care regimens, pain, and functional impairment. Mortality data was also assessed in these patients. This study revealed that the presence of depression had a significant impact on functioning and diabetes symptoms. Patients with depression also had increased mortality rates over 3 years compared with those patients who did not suffer depression.

Marta Novak (Semmelweis University, Budapest, Hungary) presented data on sleep disorders and depression in patients following kidney transplantation for end-stage renal disease. Questionnaires for quality of life, depression, and sleep disorders were used to assess 183 dialysis patients on a waiting list for kidney transplant and 884 patients who had received transplants. The results revealed that depression was more prevalent in patients who had received transplants than in those on the waiting list. The presence of depression also predicted the combined outcome of graft and patient survival after 2 years. Insomnia was again associated with depression in this population and subsequent analysis showed that restless legs syndrome (RLS), high risk for OSA, and severity of depression were all independently associated with insomnia.

The symposium concluded with Colin Shapiro (University Health Network, Toronto Western Hospital, Toronto, ON, Canada) offering comments on the interaction between fatigue, sleep disruption, and depression. Recent research was cited regarding the differences between fatigue and sleepiness and the increased likelihood of depression relapse when sleep disruption and fatigue are not treated fully.

### Night-eating syndrome

In a symposium on eating disorders, James E Mitchell (Fargo, ND, USA) offered evidence from several data pools on night-eating syndrome. This syndrome is still in the process of being definitively characterized but generally includes features of insomnia, morning anorexia, evening hyperphagia, and anxious feelings at bedtime. Findings were presented from, among other data sets, interviews of 62 night-eaters and questionnaires on night-eating given to 1479 people. The data suggest that reports of initial insomnia, arousal at night, nocturnal hyperphagia, and nocturnal eating all are precise characteristics for identifying people with night-time eating disorder. Other measured variables, such as delayed morning meal and morning anorexia did not show strong precision in identifying people with this disorder.

## Fearful sleep arousals

A symposium was held on fearful sleep arousals wherein new research on sleep paralysis disorder, nocturnal panic attacks, recurrent nightmares, and night terrors was presented. Steve Woodward (National Center for Post-traumatic stress disorder, Menio Park, CA, USA) discussed new data on the relationship between post-traumatic stress disorder (PTSD), nightmares, and the movement suppression index central fear system. It has been observed that fear of predation has a substantial role in the sleep behavior of chimpanzees. The speaker noted that neural structures known to be involved in regulation of sleep received projections from the central nucleus of the amygdale, an area of the brain known as the executive center of the "central fear system". Previous research has shown the paradoxical finding that individuals with PTSD have few objective changes in sleep, as observed in sleep laboratories, despite subjective complaints of sleep problems. Evidence was offered suggesting that subjects with PTSD have less gross body movements than those without the disorder. The speaker proposed that this finding is compatible with the influence of the central fear system on sleep.

Rosalind Cartwright (Rush University Medical Center, Chicago, IL, USA) reviewed sleep terrors and sleepwalking. These parasomnias occur due to partial arousal during the transition from non-REM to REM sleep, typically during the first 3 h of the sleep period. Studies estimate a prevalence of 15% in children, and this decreases during adolescence. Parasomnias are equally distributed between the sexes in children, but are four times more likely to be present in adult males than females. Men are also more likely to have sexual or aggressive behavior as part of the parasomnias. Parasomnias are more prevalent in individuals with a family history of such behavior, and there is some evidence of genetic inheritance from research on the *DQB1 05* and *04* genes. Sleep studies show that many patients with sleepwalking or sleep terrors have abrupt arousals from delta sleep. Ravi Singareddy (Penn State University) presented new research on nocturnal panic attacks (NPAs). These are panic attacks that take place during sleep and occur in 65% of patients with panic disorder. The speaker examined the subjective experience of sleep and depression in a cohort of people with panic attacks. In 773 individuals with panic disorder, 60.9% remember having at least one NPA. Those subjects who reported at least one NPA were more likely to be female, have a history of depression, sleep fewer hours, and have anxiety that impacts sleep. Among the subjects with panic disorder and a history of depression, those who had NPAs were more likely to sleep less and suffer from insomnia.

The symposium concluded with a presentation by Thomas Uhde (Penn State College of Medicine), who

highlighted research on the relationship between sleep paralysis and NPAs. NPAs can sometimes cause conditioned fear responses and may lead to avoidance behaviors and fear of sleep, resulting in sleep deprivation. Sleep deprivation may actually increase the severity and frequency of panic attacks, both nocturnally and during the daytime. Dr Uhde presented research conducted at Penn State College of Medicine that yielded data suggesting recurrent sleep paralysis has been under-recognized by mental health professionals and can be a disabling condition to the patient.

## Sleep deprivation

The final sleep medicine symposium focused on sleep deprivation. Dr Uhde offered a review of the differential diagnoses of sleep deprivation and its negative consequences upon public health. Dr Vgontzas continued with a presentation discussing the effects of sleep deprivation on the immune and stress systems. Utilizing sleep electroencephalograph recordings, performance, and behavioral measures, he showed data on the effects of sleep loss from a large pool of subjects. Evaluations of 24-h serial levels were also obtained for various proinflammatory cytokines and stress hormones. This data revealed that as little as 2 h of sleep loss in 1 week was sufficient to increase levels of proinflammatory cytokines, including IL-6. Although sleep loss was not associated with increased levels of cortisol, levels were reduced in the recovery sleep following sleep loss. Performance and alertness tests revealed significant impairment with a nightly sleep loss of 2 h during 1 week. A 2-h nap was sufficient to restore much of these deficits, as well as to help restore IL-6 and cortisol levels after the nap. These findings suggest even modest sleep deprivation may have adverse effects on health and longevity in addition to cognitive function.

Robert M Post (NIMH/NIH, Bethesda, MD, USA) spoke on the antidepressant effects of sleep deprivation. An entire night of sleep deprivation has been shown to have antidepressant effects in patients with depression. It is also known that increases in thyroid stimulating hormone (TSH) levels often correlate with the degree of improvement in depressive symptoms reported with sleep deprivation. This suggests that the antidepressant effect experienced with sleep deprivation may be accounted for by the release of TSH and similar factors.

The symposium concluded with a discussion by Bernadette M Cortese (Penn State College of Medicine) on PTSD and sleep deprivation. Patients with PTSD often report sleep disturbances; however, the notion that these symptoms are merely secondary to the PTSD has not been substantiated by published research. The speaker offered evidence from prospective studies for another possibility: that sleep disturbances are a primary mechanism contributing to the development of PTSD.

# 20th Anniversary Meeting of the Associated Professional Sleep Societies (APSS), LLC

Salt Lake City, UT, USA, June 17–22, 2006

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The 20th Anniversary Meeting of the Associated Professional Sleep Societies, LLC, was held in Salt Lake City, UT, USA from June 17–22, 2006. The meeting was a collaborative effort between the American Academy of Sleep Medicine and the Sleep Research Society to help promote knowledge of “sleep medicine to sleep medicine physicians, researchers, technologists, and professionals worldwide”. Over 5000 attendees were able to listen to lectures from 10 invited speakers and participate in over 120 sessions and other industry-sponsored events.

The keynote speaker was pre-eminent author and researcher, Allan Pack (University of Pennsylvania, Philadelphia, PA, USA). His past research interests have included sleepiness in older adults and the neurobiological processes of obstructive sleep apnea. His current investigations concentrate on the molecular mechanisms of sleepiness and the genetics of sleep disorders. In a session that was attended beyond seating capacity, Dr Pack discussed “The Impact of Genomics on the Future of Sleep medicine”.

The panel of invited lecturers offered diverse insights into sleep. Talks included “Stress and Sleep Quality” (Torijborn Akerstedt, University of Stockholm, Stockholm, Sweden), “Insomnia Definitions, Diagnosis and Assessment: Where do we go from here?” (Jack Edinger, Duke University Medical Center, Durham, NC, USA), “Computer Analysis of the Cyclic Alternating Pattern: Theoretical and Clinical Perspectives” (Raffaele Ferri, Oasi Institute for Research on Mental Retardation and Brain Aging, Troina, Italy), “Congenital Central Hypoventilation Syndrome: From Patients to Gene Discovery” (Claude Gaultier, McGill University, Montreal, QC, Canada), and “Structural and Functional Imaging in Normal and Disordered Sleep” (Ronald Harper, University of California, Los Angeles, LA, USA).

James Krueger (Washington State University, Pullman, WA, USA), who received the Sleep Research Society Distinguished Scientist Award spoke on “Influenza, Cytokines,

and Brain Organization of Sleep”. Gilles LaVigne (Université de Montréal, Montreal, Canada) discussed sleep bruxism and Louis Ptácek (Howard Hughes Medical Institute, University of California, San Francisco, CA, USA) gave an overview of “Genetics, Circadian Rhythms and Sleep Disorders”. David Rye (Emory University, Atlanta, Georgia, GA, USA) presented “A Quest for Restless Legs Syndrome (RLS): From Bedside to Bench, to Iceland, and Beyond” and Virend Somers (Mayo Clinic College of Medicine, Rochester, MN, USA) lectured on “Sleep and the Heart”.

## Restless Legs Syndrome

Richard Allen (Johns Hopkins School of Medicine, Baltimore, MD, USA) and Philip M Becker (Sleep Medicine Associates of Texas, Dallas, TX, USA) chaired the clinical workshop “Evaluation and Management of RLS and Periodic Leg Movements: From Childhood to the Senior”. Dr Allen presented data from probands of RLS families and suggested a distinction between “early-onset” – those presenting with primary RLS symptoms <45 years of age, and “late-onset” – presenting at ≥45 years of age. Community controls were used during the two clinical interviews. The first-degree relatives were classified into four groups depending on telephone diagnostic assessments of RLS: definite, probable, possible, and not RLS. First-degree relatives of RLS patients had a significantly greater risk of RLS than those of control subjects ( $p < 0.001$ ). Additionally, the risk of RLS was found to be greater for first-degree relatives of early-onset, rather than late-onset, RLS probands ( $p < 0.001$ ). The first-degree relatives of early-onset RLS patients were at 6.7-fold higher risk of developing RLS, whereas those of late-onset RLS patients were at 2.9-fold higher risk.

Dr Becker discussed the worldwide prevalence of RLS reported to date; with a 7.6% prevalence in the US, 4.9% in Spain, and 0.1% in Singapore (Singapore is the only Asian country reporting RLS data thus far). With an aging

population, particularly in Western countries, Dr Becker projected increased prevalence rates at these sites by the year 2050. He cited the paucity of data on RLS and periodic limb movements in sleep (PLMS) in cognitively impaired adults, with only six original articles but 26 reviews on this topic. Dr Becker also emphasized the difficulty of cognitively-impaired individuals, such as post-stroke or dementia patients, to verbalize RLS symptoms as is required as part of the current RLS criteria used by the international community. Thus, he suggested that family members of the affected individual should report a prior history consistent with RLS and suspicion or presence of the four essential criteria of RLS. Restlessness or "activation" present at rest that further worsens around evening or nighttime would also raise the possibility of RLS. Additionally, if a small dose of carbi-levodopa was found to decrease evening restlessness, then RLS could be a possible contributor to the agitation.

Dr Ferri proposed interpreting PLMS with a "Periodicity Index" that divides the number of PLMS sequences  $\geq 10$  s but  $\leq 90$  s by the total number of intervals, and reported "periodicity" of PLMS in patients with RLS or narcolepsy by this method. However, he discovered a combined age effect to the periodicity in RLS subjects that was difficult to exclude. Further research, especially with a larger sample size in the pediatric population, will help determine the validity of this index.

Jacques Montplaisir (McGill University) reported prevalence rates of PLMS in "normal" subjects aged 5 to  $>60$  years, lowest prevalence was seen in the aged 30–39 years group. While the mean PLM index was  $2.6 \pm 3.1/h$  for the aged 5–39 years group, there was an abrupt rise after the age of 40 years, with the mean PLM index being  $9.6 \pm 14.1/h$ . Dr Montplaisir also reported little periodicity in PLMS for subjects aged  $<40$  years, but periodicity was seen in those  $>40$  years. Furthermore, the interval of periodicity was shorter in the older subjects. For example, the periodicity of those aged 40–60 years was approximately 29 s, but for those aged  $>60$  years, it was shortened to 20 s. Thus, older normal individuals had PLMS in shorter intervals. Similarly, when examining the rates of PLM during wakefulness (PLMW), the presenter found that PLMW decreased with age in normal individuals. However, in RLS patients, the PLMW prevalence remained high in every group from aged 21 years onwards. This may therefore be used as a possible method for confirming a clinical history of RLS.

Daniel Picchetti (University of Illinois School of Medicine and Carle Clinic Association, Urbana, IL, USA) discussed RLS and PLMS in children. He studied data from 10 523 families in a population survey. The prevalence rate of RLS was 1.9% among 8–11 year-olds; this was classed as moderate to severe distress at least twice a week in 0.5%. In subjects

aged 12–17 years, the prevalence rate was 2.0%, with 1.0% experiencing moderate to severe distress at least twice a week. Of the children aged 8–17 years, 71.4% had at least one parent affected by RLS. This rose to 80.0% in the group aged 12–17 years. A review of normative data showed a mean PLM disorder (PLMD) index range of 0.7–2.8/h. Dr Picchetti therefore suggested that investigations into sleep disturbances should be conducted in children with PLMS of  $\geq 5$  h.

Christopher Earley and Wayne Hening (The Johns Hopkins Center for RLS, Johns Hopkins School of Medicine) conducted a clinical workshop entitled "Advanced Workshop in Management of RLS and PLMD". During this workshop, Mauro Manconi (Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Cagliari, Cagliari, Italy) discussed the limited data on this topic, and provided suggested guidelines based on case study results as treatment options for pregnant women. There are no data available regarding the use of newer dopamine agonist agents. However, according to existing data on women who were pregnant while medicated with dopamine agonists, these agents appear to be safe apart from a possible decrease in lactation. Again, there was no current data specifically regarding the use of benzodiazepines for the treatment of RLS in pregnancy. In pregnant women who were treated for anxiety disorders with clonazepam, case reports indicate efficacy without significant adverse effects. Since the majority of the women presenting with idiopathic RLS resolve spontaneously upon delivery, the presenter recommended conservative treatment or watchful waiting. The presenter suggested the following algorithm for those with more severe symptoms: during the first trimester, treatment is not recommended because of possible mutagenic effects on the unborn fetus; sleep hygiene education should be attempted. In the second and third trimesters, conservative treatment should be attempted first; if symptoms persist and ferritin level is low, this should be replaced with orally-administered iron. If this is unsuccessful, then intravenous iron replacement should be considered; however, the possible allergic side effects of intravenous iron were emphasized. For those with normal ferritin and severe symptoms, which was reportedly 1–3% of pregnant patients, the use of a dopamine agonist or benzodiazepine may be justified. The newer dopamine agonists had better adverse-effect profiles compared with older agents of the same class. Pergolide was associated with orthostatic hypotension changes, and thus, was less desirable for pregnant mothers. Anticonvulsants such as carbamazepine were associated with fetal facial abnormalities when given for seizure prophylaxis. The presenter therefore did not recommend carbamazepine, even for use in the third

trimester. As other anticonvulsant agents tend to have sedation side effects, their use was cautioned against. He also strongly recommended use of a dopamine agonist or clonazepam when necessary to limit the fetal exposure to either class of medication.

## Women and sleep

A symposium of much interest was "Gender and Sleep: From Bench to Bedside", chaired by Aaron Laposky (Northwestern University, Evanston, IL, USA). Dr Laposky's review of the literature revealed that estrogen has varying effects on sleep. In rats, it appeared to suppress rapid-eye movement (REM) sleep, whereas progesterone had a benzodiazepine-like sedation effect and potentiated non-REM (NREM) sleep.

Ketema Paul (Georgia State University, Atlanta, GA, USA) discussed gender-specific findings in a mouse model. The procedures performed included sleep deprivation 1 h before light phase, forced restraint protocol, and then allowing for recovery sleep. Female mice slept for 1.5 h more during a 24-h period than the males. There were no observed gender differences in REM sleep during light or dark cycles. There was slight increase in wakefulness over the 24-h cycle in castrated males and a slight decrease in wakefulness in ovariectomized females over the same period; however, these results were not significant. There was also a similarly slight increase in NREM sleep in female ovariectomized mice. Dr Paul concluded that female mice had better consolidation of sleep architecture to sleep deprivation challenges, with fewer arousals and decreased wake duration. Gonadectomy decreased the gender differences seen in the amount of NREM recovery sleep in response to sleep deprivation and, in castrated males only, further accentuated REM sleep recovery. Based on previous work, Dr Paul concluded that sleep regulation in female mice was primarily influenced by genetic background and, to a lesser extent, by hormonal variations associated with the estrous cycle.

Axel Steiger, (Max Planck Institute of Psychiatry, Munich, Germany) presented new data from transgender subjects. Ten men, undergoing processes preceding transgender surgery, were given chronic estrogen (80–100 mg/day), and progesterone (300 mg/day), or placebo for 21 days. Polysomnographic (PSG) data revealed an increase in stage-1 sleep, decreased time awake, and an increase in REM sleep time in those receiving hormones compared with those given placebo. Combined estrogen and progesterone appeared to help sleep maintenance in this population.

Tarja Porkka-Heiskanen (University of Helsinki, Helsinki, Finland) reviewed "Human Sex Differences in Sleep across the Lifespan". Of the 8800 women questioned in the UK during

2000, those who were in the lower socioeconomic strata reported more sleep complaints. However, women with a college education or above did not show any sleep advantage over their less-educated peers. Thus, although higher income and educational level was beneficial to women in terms of sleep complaints, beyond a certain point it appeared to be of selectively more benefit for men than women. Having a spouse who snored affected sleep in >40% of the women questioned. The presenter advocated examining sleep in women in the context of social and environmental pressures.

Dr Porkka-Heiskanen also discussed the study of Polo-Kantola and colleagues [1]. After sleep deprivation, women who did not use hormonal replacement supplements (non-hormone replacement therapy [non-HRT] group), had a decreased ability to discharge sleep pressure, as represented by delta sleep on nocturnal PSG. Women in the HRT group had a "smaller sleep debt", less recovery during the first NREM cycle, but continue to recover sleep during subsequent NREM cycles throughout the night. Women receiving HRT were seen to have an improved reaction time and fewer errors (assessed using the psychomotor vigilance task [PVT]), when compared with young women and women not receiving HRT.

Roseanne Armitage (University of Michigan, Ann Arbor, USA) discussed "Human Sex Differences in Sleep-Related Disorders". She began by summarizing the current understanding of gender differences in human brain structure and sleep. Men were described as having smaller corpus callosa and anterior commissure. Men have a lower cerebral metabolism compared with women, and smaller asymmetries were observed during task performance measures. Thus, men were reported to be more of a "serial information processor rather than parallel". Women were found to have more estrogen receptors in the suprachiasmatic nucleus and throughout the hypothalamus. Oral contraceptives in women reportedly decrease REM latency, increase REM time, increase time awake, and decrease slow wave sleep (SWS).

Dr Armitage reported results of 40-h sleep deprivation in healthy subjects aged 19–20 years. In general, female subjects showed a greater response in SWS, while 50% of men did not. It was hypothesized that women may have a more "flexible, adaptive" biological response and biological clock compared with men. Interestingly, she found that suburban living conferred an increased depression risk for women, but a decreased risk for men. When examining a 3-h sleep delay on slow wave activity (SWA) relative to baseline, Dr Armitage discovered that depressed women had the greatest response compared with healthy controls and depressed men [2,3]. Depressed men had the lowest SWA response. Thus, she concluded that the "adaptive response



was greater in women, which created a homeostatic hyper-response in women, but a hypo-response in men". Alternatively, there may be a gender-dependent response to biological challenges. Seemingly, by having a more adaptive system, women are more likely to be able to cope with various hormonal, biological, and environmental stressors in their lifetime.

## Neurology in sleep

The "Sleep in Neurological Disorders" session, chaired by Claudio Bassetti (University Hospital Zurich, Zurich, Switzerland) and Rosalia Silvestri (Università di Messina, Messina, Italy), comprised of discussions on sleep and headaches, sleep and stroke, sleep in narcolepsy and CNS hypersomnolence, and sleep and epilepsy.

Dr Silvestri reviewed hypotheses regarding migraine, cluster, and hypnic headaches. Possible associations with sleep-disordered breathing were explored, and other clinical features were contrasted; for example, cluster headaches were reportedly to be highly associated with REM sleep, illustrating the circadian rhythmicity of these headaches. Treatment options were briefly mentioned, and identification of possible confounders such as obstructive sleep apnea (OSA) was advocated. In studies during 1983 and 1986 involving pediatric migraine patients, a 30% prevalence of somnambulism was reported [4,5]. Thereafter, the serotonergic hypothesis was presented: medullary 5-hydroxytryptamine neurons are in close proximity to large blood vessels, which would allow rapid sensing of an increase in serum carbon dioxide and it is thought that metabolic acidosis might induce somnambulism. Whether these two processes are linked or mere coincidental occurrences precipitated by another process such as an arousal disorder is as yet unknown.

Vahid Moshenin (Yale University, New Haven, CT, USA) presented data on the association of snoring and stroke. According to the results of the Sleep Heart Health Study, the prevalence of stroke/transient ischemic attack (TIA) increases with the severity of OSA; when the respiratory disturbance index exceeded 11.0/h (from a baseline of 0–1.3/h), the odds ratio (OR) for TIA increased to 1.55 [6]. The Wisconsin cohort (a population-based cross-sectional epidemiological study of adults aged 30–60 years) similarly witnessed a 300% increase in the risk of a cerebrovascular event (CVA) in a 4-year period for those with an apnea–hypopnea index >20/h after adjusting for age, sex, and body–mass index (BMI) [7]. The Yale cohort, reported in the *New England Journal of Medicine* in 2005 demonstrated a similar trend [8]. Using the Barthel index (which helps quantify progress in rehabilitation), patients who had OSA and suffered a CVA/TIA event were shown

to have poorer functional status 12-months post-recovery compared with their non-OSA peers.

Dr Bassetti summarized typical symptoms and presentations of individuals affected by narcolepsy and idiopathic hypersomnia. An intriguing finding was that stimulation of the parietal lobe can induce an out-of-body experience. Thus, the narcolepsy symptom complex could be secondary, in relation to sleep–wake instability, to disturbance of the integration of multi-sensory information.

Lino Nobili (Niguarda Hospital, Milan, Italy) primarily focused on nocturnal frontal-lobe epilepsy (NFLE). With successful implantation of intracerebral leads, PSG detection significantly improved the detection of NFLE compared with scalp electroencephalogram (EEG). Epileptic discharges were demonstrated to correlate with atypical, non-stereotypical movements on video monitoring. While typical dystonic movements of the lower limbs were exhibited by some of the patients, other movements by the same patients included touching of the face, abrupt arousals, shifting of body positions, or rubbing of the legs. Dr Nobili proposed the ensuing classification of these movements:

- Major events, including nocturnal dystonic movements.
- Paroxysmal arousals, usually lasting 5–10 s with head elevation, often with vocalization.
- Minor events, 2–4 s movements of the limbs, bruxism, touching the face, or movement of the truck.
- Epileptic nocturnal wanderings.

Nevertheless, arousals from other causes such as OSA should be considered in the differential diagnosis. Although diagnosis has been made easier, medical treatment remains difficult for the non-surgical candidates.

## Kleine–Levin Syndrome

An interesting symposium, "New Developments in Kleine–Levin Syndrome (KLS)" was co-chaired by Isabelle Arnulf (Stanford University Center for Narcolepsy, Palo Alto, CA, USA) and Yves Dauvilliers (La Colombiere Hospital, Montpellier, France). KLS affects children and teenagers (onset age 10–25 years) with periods of hypersomnia, hyperphagia, and occasionally hypersexuality. Boys are affected more often than girls, and frequently there is a sense of detachment from reality during attacks. Dr Arnulf and Emmanuel Mignot (Stanford University School of Medicine, Stanford, CA, USA) discussed their collaborative results. A systematic review of the literature was performed by the Stanford group [9]. Of 108 patients with KLS, 72% had an infection preceding its onset, 23% had used alcohol, 22% reported sleep deprivation, and a smaller proportion had "unusual stress". The mean total sleep time over the

duration of illness was 17.9±3.6 h (range 14.7±4.8 to 21.4±2.5 h). Depressed mood was seen in 48% of those affected, and increased sex drive was seen more frequently in boys (58.5%). Mean duration of a symptomatic period was 13 days, with a maximum of 365 days. There was a mean 19 episodes/year, and mean interval between episodes was 5.7 months (range 0.5–66 months). The median duration of symptoms was 13.6±4.3 years, and adult-onset subjects had the longest duration of KLS. No serum markers of this condition have been found. In this case series, after adjusting for BMI in the KLS group, the differences in leptin and C-reactive protein (relative to the control group) were no longer significant.

While in Dr Arnulf's group amantadine produced a partial benefit as reported by patients, this has not been found by other groups [9]. In 50% of the patients, bupropion yielded self-reported partial benefit, and similarly, 37% of patients treated with risperidone had partial benefit. No benefits of corticosteroids, acyclovir, or carbamazepine were found. Lithium and valproic acid produced a "mild" benefit. Amantadine had a more subjective benefit compared with methylphenidate or modafinil. Dr Mignot presented the genetics of 15 familial cases. Amongst the eight siblings, three parent-child pairs, three cousins, and one avuncular case, there was more likely to be a history of birth difficulties (25% vs. 7.4%), developmental delay (14.8% vs. 0%), or either problem, compared with control subjects ( $p=0.0005$ , OR 4.2). Human leukocyte antigen allele DQB1\*02 (0201, 0202) were found in 17 KLS cases (28.3%) compared with eight controls (12.5%,  $\chi^2$  4.82,  $p\leq 0.03$ ). More intriguingly, amongst the US cases, 10 were of Jewish ethnic origin.

Further work on this syndrome was presented by Natan Gadoth (Meir General Hospital Kfar-Saba and the Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel). The Israeli series spanned 1978–2002. Of the 34 patients with KLS who were studied, 29 were of Ashkenazi origin. The onset age of KLS was 15.8±2.8 years (range 9–21 years), length of attack duration was 11.5±6.6 days (range 3–42 days), and number of yearly attacks was 7.5±6.2 (range 2–25). PSG results showed a decrease in sleep efficiency, frequent awakenings from stage-2 sleep, and an increase in total sleep time for 18 KLS patients during attacks and in 17 patients during symptom-free periods, compared with normative data. Of the 40 patients with a history of possible precipitants, 24 had none, 10 had intermittent febrile illnesses, three had moved from colder to warmer climates, two had emotional stress, and one had panic attacks.

Medications that caused no improvement included methylphenidate, pemoline, tricyclic antidepressants, selective serotonin reuptake inhibitors, anticonvulsants, flumazenil, lithium, and melatonin. Intravenous amantadine also failed to produce a significant response. Of the 28 patients available for follow-up, the mean time to recovery was 4.1 years (range 1–8 years).

Yu-Shu Huang (Chang-Gung University Hospital, Taipei, Taiwan) presented imaging information of patients with KLS. Five subjects were studied during symptomatic periods, and seven were symptom-free. Serum and other laboratory tests were negative. Magnetic resonance imaging and computed tomography (CT) of the brain revealed nothing remarkable. Single photon emission CT scans showed that five subjects had hypoperfusion of the thalamus and four of five had hypoperfusion in the basal ganglia. Dr Huang suggested that more diffuse areas of involvement could be the result of a more prolonged disease process. Thus, this is an interesting and debilitating syndrome without any known effective treatment, although medical progress has enabled us to become closer to understanding this syndrome than previously imagined.

## Summary

Other important topics covered at the 20th APSS meeting included discussion groups of the new guidelines for pediatric sudden infant death syndrome, normal breathing in children, new detection methods and further study of OSA in children, effects of sleep deprivation on cognition and its role in obesity, insomnia, parasomnia, and sleep bruxism. This meeting provided a diverse and enriching learning experience for sleep professionals.

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