Neurologists see sleepy patients but often have limited facilities to investigate them. This article provides an update on the conditions causing sleepiness and describes how to investigate and manage sleepy patients.

OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME

The obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is the most common medical cause of sleepiness. It can present at any age but is most common in middle age, when it occurs in around 1–4% of men and 1–2% of women. It occurs rarely in the teens and 20s—a useful differentiator from narcolepsy. Patients usually present with sleepiness which is sometimes irresistible, but often causes difficulty with concentration and work performance rather than sleep attacks. Patients typically find sleepiness most troublesome in monotonous situations such as driving on motorways, reading, and watching television. OSAHS patients usually feel their sleep is undisturbed but do not feel refreshed in the morning. Their partners report loud snoring, apnoeas, and restless sleep. Two thirds of OSAHS patients are men and 50% are obese (body mass index > 30 kg/m²). Retrognathia plays a significant role, particularly in the non-obese.

OSAHS is caused by the throat becoming critically narrow during sleep. Pharyngeal patency is usually achieved by the phasic contraction of upper airway dilating muscles during each inspiration, thus resisting sucking the throat shut as air is sucked in. There is no evidence of upper airway muscle dysfunction in OSAHS, rather the abnormality is anatomical—patients have narrower pharynxes than the normal population when awake. Thus, the physiological relaxation of the palatal and tongue muscles during sleep results in pathological throat narrowing. The patient then struggles to overcome the obstruction until aroused by negative intrathoracic pressure. The brief arousal reactivates the upper airway dilating muscles, and a few unobstructed breaths are taken before sleep resumes and apnoea recurs. This cycle of apnoea, arousal, apnoea, arousal may recur many hundreds of times in the night and the sleep fragmentation causes the sleepiness.

There is now unequivocal evidence that OSAHS causes an increased risk of road accidents—perhaps sixfold—and of hypertension independent of comorbidities such as obesity. There is also firm evidence that treating OSAHS reduces road accidents and blood pressure.

Investigating OSAHS

Patients whose sleepiness is impairing their quality of life, work performance or driving safety and who have no other obvious explanation for being sleepy require overnight study of their breathing and oxygenation during sleep. Most such patients will snore but, as no snoring history can be obtained in some, even alleged non-snorers should be investigated in this way if they have a normal nocturnal sleep duration and no cataplexy. The complexity of diagnostic test used is not so important as the knowledge of the interpreting physician. In severely hypoxaemic patients, overnight oximetry alone may suffice, but a normal oximetry or normal limited respiratory sleep study will not exclude the diagnosis and more complex investigation may be needed, up to the level of overnight neurophysiological monitoring (polysomnography) in some. The so-called upper airway resistance syndrome probably does not exist but results from inadequate diagnostic methodology.

Treating OSAHS

Weight loss when appropriate and alcohol avoidance are the first steps of treatment, but most individuals with significant sleepiness will require continuous positive airway pressure (CPAP) therapy and the evidence base for CPAP efficacy is now robust. Indeed, in terms of effect size of benefit, CPAP is one of the most effective forms of treatment in medicine. Mandibular repositioning splints have a role as second line treatment for patients with mild OSAHS who cannot tolerate CPAP. While there is no robust evidence base in favour of orthonoinaryngological approaches, including uvulopalatopharyngoplasty (UPPP), there is good evidence that maxillomandibular advancement surgery can provide a “one-off” cure in some cases.
Narcolepsy

Cataplexy is the most specific of the classical tetrad of narcolepsy—sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Sleep paralysis and hypnagogic hallucinations occur in several sleep disorders and sleep paralysis occurs in normal young adults with irregular sleep times. The features of narcolepsy usually begin in the teens or 20s although they may start as early as 2 years old. However, delay in obtaining diagnosis means the diagnosis is often made a decade or more after symptoms start. Onset after 50 years is unusual. Narcolepsy is about 1/100th as common as OSAHS, occurring in 20–50 per 100 000.

Sleepiness

The sleepiness is most pronounced in the usual soporific situations, but many narcoleptics get irresistible sleep attacks in bizarre situations, such as eating or walking.

Cataplexy

Cataplexy is the sudden decrease or loss of voluntary muscle tone following emotion, usually laughter or sometimes anger. Typically, the jaw drops, the head nods, the arms drop to the side and the knees sag, but partial attacks are common and some attacks may be limited to head nodding. The presence of facial twitching during attacks is a useful pointer.

Cataplectic episodes usually last only a few seconds but can last up to 10 minutes and awareness continues throughout the attacks.

HLA type

Over 85% of whites and Japanese narcoleptics are HLA DR2 DQw1 positive. However, in African Americans, DR2 occurs in only 75%, while the association with DQw1 is as strong as in whites. Genomic mapping of the HLA DQw1 region shows that the DQB1 0602 allele is closely linked with narcolepsy and is positive in 84–95% of narcoleptics with clear cataplexy. However, it is present in around 22% of the normal white population and in 40% of the normal black population, and so is of little diagnostic specificity.

Gene defects

Doberman dogs can have familial narcolepsy with sleepiness and cataplexy and this is associated with a gene mutation causing a deletion in the transcript of the hypocretin type 2 receptor, Hcrt2. Hcrt gene knock-out mice exhibit episodes of behavioural arrest which probably represent cataplexy. However, human narcolepsy is rarely familial; twin studies show discordance and narcoleptics do not appear to have defects in their hypocretin receptor genes. Thus, the relevance of these gene abnormalities to human narcolepsy is unclear and environmental factors may be important.

Hypocretin concentrations were undetectable in seven of nine patients with narcolepsy, and hypocretin producing neurones reduced by around 90% in narcoleptic hypothalamai. The association of narcolepsy with HLA types has led to the suggestion that it is an autoimmune disease which results in destruction of hypocretin producing cells, analogous to insulin dependent diabetes, but this is unproved.

Investigation of narcolepsy

The multiple sleep latency test (MSLT) is the most useful diagnostic test. The classical teaching is that the mean sleep latency is usually < 8 mins, compared with > 10 mins in normal individuals, and that sleep onset rapid eye movement (SO-REM), defined as REM sleep within 15 mins of sleep onset, is common in narcolepsy. A < 8 min mean sleep latency with 2 SO-REM periods is clinically helpful when present, but may occur in OSAHS, periodic limb movement disorder, circadian rhythm disturbances, and REM sleep deprivation, and in up to 12% of normals. Conversely, only 71% of narcoleptics with cataplexy have a mean sleep latency of < 8 mins and two or more SO-REM on initial MSLT; even after repeated MSLTs, this will not rise above 80%. Thus, not all narcoleptics show the classical changes.

However, I find the MSLT diagnostically helpful. A positive MSLT in conjunction with the appropriate history is strong evidence in support of the diagnosis. Further, I believe every effort should be made to confirm the diagnosis before embarking on potentially lifelong therapy with drugs which may be addictive. Another reason for doing MSLTs routinely is that the increasing publicity for narcolepsy has resulted in cases of Munchausen’s syndrome presenting with classical features of narcolepsy but with normal MSLTs, and patients who fail to sleep at all on an MSLT do not have narcolepsy.

Treatment of narcolepsy

Optimising nocturnal sleep duration and planned daytime naps remain the cornerstones of treatment. Almost all patients will require medication for their sleepiness and/or their REM sleep intrusion phenomenon.

Sleepiness

The choice of stimulant to use in any particular patient is a balance between benefits and side effects, and trial and error is usually required. Unfortunately, most patients cannot achieve full alertness because of side effects. I start with milder drugs with fewer side effects and work down this list until the side effect:benefit ratio is optimised. The order I use (and daily dose) is: modafinil (200–800 mg), mazindol (2–8 mg), methyl-phenidate (10–100 mg), selegiline (2.5–10 mg) and, finally, dexamphetamine (5–60 mg).

Modafinil is the agent with greatest “evidence based medicine” backing therapeutic efficacy but there have been no head-to-head trials with other agents.

REM intrusive phenomena

Cataplexy, sleep paralysis, and hypnagogic hallucinations can all be treated with antidepressants. Fluoxetine 20–40 mg daily is probably the current treatment of choice, although protriptyline 5–30 mg daily, clomipramine 20–200 mg daily or imipramine 50–250 mg daily may also be effective. Several drugs may need to be tried before optimal control is achieved.

Periodic limb movement disorder

This ill defined condition is an association between recurrent limb movements every 20–40 seconds during non-REM sleep and daytime sleepiness, frequent nocturnal awakenings or difficulty initiating sleep. Most people with periodic limb movements during sleep (PLMS) are asymptomatic and PLMS are extremely common, occurring in 30% of 50–65 year olds and nearly 50% of over 65 year olds. Although PLMS are associated with evidence of arousal—albeit sometimes not detectable on the electroencephalogram (EEG)—there is no correlation between periodic limb movements and sleepiness.

Periodic limb movement disorder (PLMD) is associated with the restless leg syndrome (RLS) which is characterised by an intense urge to move the legs and motor restlessness which are worse in the evening or night. There are placebo controlled studies showing better subjective sleep in patients with RLS after L-dopa or pergolide, but there have been no adequate trials of any treatment in PLMD in the absence of
restless legs. It is thus questionable whether it is necessary to investigate sleepy individuals for PLMD in the absence of RLS, or whether PLMD even exists as a distinct syndrome.

**Idiopathic hypersomnolence**

Idiopathic hypersomnolence was named before OSAHS was identified. As idiopathic hypersomnolence is a diagnosis of exclusion, the condition has gradually become less common and is now believed to affect around 4 per 100,000, a prevalence 1/10th that of narcolepsy and 1/1000th that of OSAHS. Nocturnal sleep is often prolonged, waking is difficult and slow, and sleep drunkenness may occur. Naps tend to be prolonged. In some, idiopathic hypersomnolence is self-limiting, resolving after several years; in others it persists.

**Diagnosis**

Being a diagnosis of exclusion, a “firm” diagnosis requires a typical history including >7 hours nocturnal sleep and a regular sleep-wake cycle plus normal overnight polysomnography, including the absence of recurrent arousals from sleep. OSAHS must be excluded. An MSLT should confirm the presence of objective sleepiness and exclude the presence of SO-REMs.

**Treatment**

Alcohol, sleep deprivation, and shift work should be avoided. Planned daytime naps are generally unhelpful and may result in confusional episodes. Sleepiness is treated using the same drugs as narcolepsy.

**Other causes of sleepiness**

**Neurological lesions**

Tumours and infarcts in the brain can cause pronounced sleepiness, particularly tumours of the hypothalamus, pineal or upper brain stem, and infarcts affecting the paramedian thalamopeduncular area. Head injuries can be followed by sustained sleepiness, usually starting within one year of the injury. Multiple sclerosis and encephalopathy may also be complicated by sleepiness.

**Psychological/psychiatric causes**

Depression is often associated with sleepiness. Some patients react to stress by increased sleepiness with or without insomnia. Usually, there is no objective sleepiness on the MSLT.

**Delayed sleep phase syndrome**

This condition is most common in adolescents and young adults and is characterised by late sleep onset with late awakening. Indeed, if the patient is left to sleep themselves, such as weekends, they will often sleep into the afternoon. These individuals complain of difficulty waking in the morning and pronounced morning sleepiness. Many cases may be associated with depression but it is not clear whether this is cause or effect. Diagnosis is from history, confirmed by actigraphy. Treatment is by gradual phase advance (by 15–30 mins every night) combined with bright light exposure on waking.

**Shift work**

Sleep disturbance caused by shift work is a major cause of sleepiness. Problems are most common in those on night or rotating shifts which result in varying sleep times. Many night shift workers revert to nocturnal sleep patterns at weekends. This difficulty is greater in older subjects. All sleepy patients should be carefully questioned about shift patterns and sleep times. Treatment with bright lights has been tried with some success.

**Intermittent sleepiness**

**Kleine-Levin syndrome**

This rare syndrome is characterised by recurrent attacks of daytime sleepiness associated with bizarre eating and sometimes with hypersexuality. The onset is usually in adolescence and the association of disturbance of sleep and sometimes temperature rhythms has led to the unsubstantiated suggestion of a hypothalamic or circadian cause. Diagnosis is helped if the patient is seen during a prolonged sleep attack which can be confirmed by EEG recording. Stimulants may reduce the severity of sleep attacks in some patients. Lithium or carbamazepine may reduce the frequency of subsequent episodes.

**Menstrually related**

Rarely, severe sleepiness may recur at the start of the menstrual cycle. This usually commences in adolescence. Oral contraceptives may be effective.

**Differential diagnosis of sleepiness**

Sleepiness must first be differentiated from muscle fatigue by detailed questioning about falling asleep or feeling sleepy, and the Epworth sleepiness scale may be useful. Sleepy patients must be asked about shift work and whether they are getting 7–8 hours sleep at night, and then psychological factors or OSAHS must be considered (see box). Other medical causes are uncommon.

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<th>Persistent sleepiness</th>
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<tr>
<td>▶ Lack of sleep</td>
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<td>– inadequate time in bed</td>
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<td>– extraneous sleep disruption, including babies/children</td>
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<td>– shift work</td>
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<td>▶ Sleep disruption</td>
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<td>– sleep apnoea/hypopnoea syndrome</td>
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<td>– periodic limb movement disorder</td>
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<tr>
<td>▶ Sleepiness with relatively normal sleep</td>
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<tr>
<td>– narcolepsy</td>
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<tr>
<td>– idiopathic hypersomnolence</td>
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<tr>
<td>– neurological cause for sleepiness</td>
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<td>– drugs</td>
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<tr>
<td>– psychological sleepiness</td>
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**Intermittent sleepiness**

| ▶ Jet lag |
| ▶ Kleine-Levin syndrome |
| ▶ Menstrually related hypersomnia |

**Investigating sleepy patients**

Everyone with sleepiness causing recurrent problems with driving or work impairment or an Epworth sleepiness score of 12 or over, despite having >7 hours to sleep in bed each night, should be investigated, unless they have varying sleep times because of shift working. How I investigate them will depend on history. **Sleepy snorers** have a home based limited sleep study without electroneurological recording. Those with >30 apnoeas plus hypopnoeas/hour in bed will proceed directly to a CPAP trial; a lower frequency will be followed by polysomnography in the sleep centre to ensure adequate sleep quality and identify other causes of sleepiness.
Limited sleep studies including oximetry alone studies cannot exclude OSAHS. Patients with a history suggesting narcolepsy (possible cataplexy or frequent sleep paralysis or hypnagogic hallucinations, onset before middle age) will have an MSLT™ following an actigraphically monitored night at home to ensure adequate sleep duration. Overnight investigation is not performed, unless the story suggests OSAHS. An MSLT < 10 mins without two SO-REMs results in overnight polysomnography—principally aimed at occult sleep apnoe/hypopnoea syndrome or RLS—and is followed by a repeat MSLT.

References