The nocturnal brain: sleep disorders and their implications

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Sleep is intimately linked with almost all aspects of our health. It is therefore crucial that clinicians have an understanding of sleep disorders, their diagnosis and management, as they are potential risk factors for a broad range of medical conditions.

A third of human life is usually spent asleep, so it is no wonder that is so important in our waking lives as well. However, medical information around sleep disorders often remains low despite its prevalence in the general population

In the wider medical community, there remains a limited understanding of sleep and its disorders, along with its significance for a broad range of physical and psychological conditions. Despite recent public attention on the subject of sleep, sleep medicine continues to be poorly taught at medical school, with only a minor increase in teaching over the last two decades: in 1998, the median time spent in medical school on sleep was 20 minutes, rising to a median of 1.5 hours in 2018.[1]

Clinicians will be familiar with common sleep disorders, such as insomnia and obstructive sleep apnoea (OSA); however, there are many, including other common conditions such as restless legs syndrome (RLS) or periodic limb movement disorder, which most doctors will have little knowledge of in terms of their presentation, pathophysiology and implications. Many of these sleep disorders will be of relevance to clinicians practising in almost every speciality, including cardiology, urology, psychiatry, respiratory medicine, neurology, anaesthetics and general practice. These sleep disorders also provide major insights into underlying neurobiological mechanisms regulating sleep in healthy individuals and, through their disruption of normal sleep, an understanding of the various aspects of sleep.[2]

Normal sleep

Sleep is not a static phenomenon. The average adult has a sleep requirement of seven to eight hours per night, but there is significant variability, in part influenced by genetic factor. Sleep requirements also vary through life. On average, newborns have a sleep requirement of 14–18 hours per night, gradually decreasing over their lifetime.

Sleep also constitutes several different brain states. It is comprised of rapid eye movement (REM) sleep and non-REM sleep. In REM sleep, the stage of sleep typically associated with dreaming, the cerebral cortex is highly active, the electroencephalogram (EEG) is desynchronised (similar to wakefulness), and sleep is accompanied by the generation of muscle atonia in all voluntary muscles with the exception of extraocular musculature (these REMs are responsible for the terminology of this stage of sleep). In non-REM sleep, classified as N1 (drowsiness), N2 (light sleep), and N3 (deep sleep), there is progressive desynchronisation on the EEG, with slowing of rhythms and the appearance of other EEG phenomena. In contrast to popular belief, dreaming is not limited to REM sleep; although, dreams in REM sleep typically have a narrative structure, with more realistic elements.

A typical adult's night will consist of cycling through the various stages of sleep four or five times, initially in gradually deepening non-REM sleep before entering REM sleep roughly 60–90 minutes after sleep onset (see Figure 1). Over the course of the night, episodes of REM sleep will become longer, and episodes of non-REM sleep will become shorter. The majority of N3 non-REM sleep occurs in the first half of the night, while the majority of REM sleep occurs in the latter half.

Two underlying biological processes influence the drive to sleep. The first is the homeostatic process (also known as Process S), whereby the drive to sleep is associated with the duration of wakefulness, and is dissipated by sleep duration and intensity, *ie* the longer one is awake, the stronger the need to sleep. The second influence is that of the circadian rhythm (also known as Process C), which is a 24-hour rhythm largely driven by oscillating outputs of the suprachiasmatic nucleus, a small region of the hypothalamus viewed as the 'master clock' of the brain. Ideally, both processes should be synchronised to result in optimal sleep, with both providing the maximal drive to sleep in the late evening, and the lowest drive to sleep in the morning.

Abnormal sleep

From a clinical perspective, sleep disorders are usually divided into three categories:

- Hypersomnias – conditions that cause either excessive daytime sleepiness or a long sleep duration;
- Parasomnias – conditions that result in abnormal unwanted behaviours arising either from or around sleep;
- Insomnias – conditions resulting in a poor subjective experience of sleep duration or quality, associated with negative daytime consequences such as fatigue, sleepiness or cognitive complaints.

However, it is important to bear in mind that some sleep disorders may give rise to two or more clinical pictures, and so the presentation should only be a guide to taking a patient's medical history and subsequent investigation. It is crucial to stress that, since sleep is a complex phenomenon that is not just influenced by neurobiological factors, much of the process of diagnosing sleep disorders revolves around the exclusion of other potential causes, such as poor sleep hygiene, chronic sleep deprivation (which affects up to 20% of the adult population), prescribed and non-prescribed drugs, and physical or psychiatric disorders. In practice this can occasionally be problematic, since sleep disorders often give rise to psychological and somatic sequelae, and drugs can have hugely variable consequences for sleep.

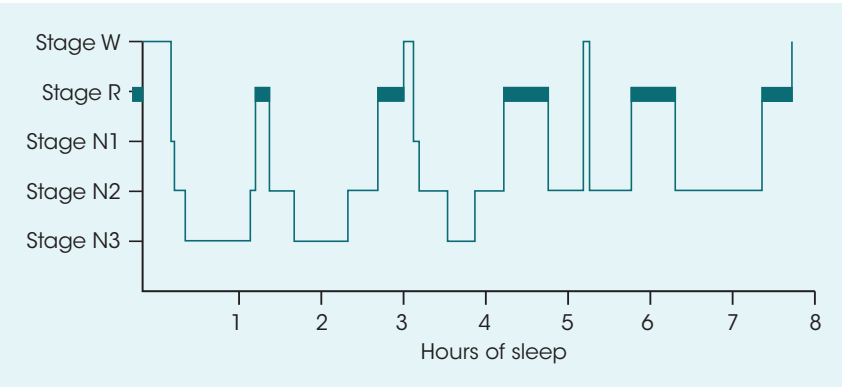

Figure 1. Example of a hypnogram for a young adult, demonstrating cycling of sleep stages between rapid-eye movement (REM) and non-REM sleep. Over the course of the night, periods of REM lengthen, and the majority of deep (N3) sleep is seen in the first half of the night

Evaluating sleep disorders

Patient history is the single most important aspect of the sleep evaluation, and the results of objective testing can be open to significant misinterpretation if not viewed in the context of the clinical picture. In addition to a patient's history, it is important to obtain a corroborative history from the patient's bed-partner (if possible), as we obviously are often poor witnesses to our own sleep.

Clinical tools such as the Epworth Sleepiness Scale (ESS)[3] (see Table 1), a subjective measure of daytime sleepiness, can be useful. This 24-point questionnaire assesses tendency to nap or sleep in eight scenarios. A very low score is usually highly indicative of a psychophysiological basis to poor sleep quality since those mechanisms that drive poor sleep at night are also present during the day, while a high score (>9/24 is considered pathological) points towards an underlying organic basis. However, the ESS should only be considered a guide, since the correlation between subjective and objective measures of sleepiness is notoriously poor. Other important aspects of a patient's history include sleep hygiene (behaviours that may affect sleep; for example, caffeine and alcohol intake, sleeping environment, shift work), sleep duration, drug and psychiatric history.

Investigations should be considered as supplementary to a patient's history in many cases. The majority of patients with insomnia do not require sleep-specific investigations and will often sleep very little when admitted. However, a number of different investigations are used in routine clinical practice. For patients in whom obstructive sleep apnoea is being considered, home-based studies, assessing overnight oxygen saturations, heart rate, and sometimes chest movements and airflow, are usually the first things investigated. Other investigations include actigraphy (the tracking of sleep patterns over several

The Epworth sleepiness scale	
Name:	
Today's date:	Your age (years):
Your sex (male = M; female = F):	
How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation: 0 = would *never* doze 1 = *slight* chance of dozing 2 = *moderate* change of dozing 3 = *high* chance of dozing	
Situation	**Chance of dozing**
Sitting and reading	
Watching TV	
Situation	
Sitting, inactive in a public place (*eg.* a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, *while stopped for a few minutes in the traffic*	

Table 1. The Epworth sleepiness scale. Reproduced with permission[3]

days or weeks using accelerometer-based technology to measure movement), full polysomnography (which assesses sleep architecture, movement and breathing), and the multiple sleep latency test (an objective measure of daytime sleepiness).

Insomnia

Insomnia is the most common sleep disorder, affecting about 10% of the population on a chronic basis. For the vast majority of cases this has a psychophysiological basis that is beyond the scope of this article, but in simple terms it relates to behavioural and cognitive practices that are not conducive to good quality sleep. Patients find themselves consciously and unconsciously associating bed with a difficulty getting to sleep. This is often associated with specific sleep-related anxiety, although in approximately 50% of individuals with insomnia there is comorbid anxiety and/or depression. There is often also a two-way relationship with psychological difficulties, in that while anxiety and depression may give rise to insomnia, poor sleep also increases the risk of anxiety and depression, and the presence of insomnia in the context of anxiety and depression makes psychiatric treatment more difficult.

Circadian rhythm disorders (for example, patients who are extreme night owls or morning larks) may mimic insomnia. Delayed sleep phase syndrome, where individuals go to sleep extremely late and wake up late, may simulate sleep initiation difficulties; while the converse, advanced sleep phase syndrome, may simulate termination insomnia. The key aspect of these conditions is that patients feel normal when they are allowed to sleep in an unrestricted pattern.

Restless legs syndrome may also prevent sleep initiation (see section on 'Hypersomnias'), but typically these patients can sleep during the day, when the RLS symptoms are less dominant. Many drugs can induce insomnia, such as certain antidepressants, steroids, anticonvulsants, thyroxine, and (obviously) stimulants. Pain and/or discomfort associated with a wide range of rheumatological, orthopaedic or neurological conditions may also disrupt sleep.

Standard treatment should include cognitive behavioural therapy for insomnia (CBTi) to re-establish the positive association between bed and sleep. This evidence-based approach, available online, in groups or on a one-to-one basis, improves sleep in the majority of individuals.[4]

Pharmacological treatments should largely be reserved for those who have not adequately responded to CBTi, due to concerns about habituation, dependency, and possible long-term complications such as increased risk of cognitive impairment and dementia. These include Z drugs, such as zopiclone or zolpidem, benzodiazepines, antihistamines or small doses of sedating antidepressants. Ideally, many of these should only be used on a short-term basis.

Although chronic sleep deprivation has been associated with numerous negative health outcomes such as metabolic syndrome, cardiovascular and cerebrovascular disease, cancer, dementia and psychological ill-health, it is important to note that this does not necessarily apply to all patients with insomnia. Many insomniacs do not have significantly curtailed objective measures of sleep, or adaptive

mechanisms that prioritise deep sleep. Some literature suggests that only those with insomnia and objective short sleep duration are at risk of these sequelae.[5]

Parasomnias

Parasomnias are unusual or unwanted behaviours at night that can usually be characterised by the stage of sleep from which they arise.

Muscle atonia is a feature of REM sleep; however, loss of REM atonia can result in enactment of dreams, termed REM sleep behaviour disorder (RBD). RBD is often seen in older individuals, and is characterised by the acting out of dreams, which often have a violent content. In the sleep clinic, it is seen approximately twice as often in men as women, although this may simply reflect referral bias due to more violent dream behaviour in males.[6] Often patients will cry out, swear or shout, and when woken will recall dreams appropriate to their actions. During events, their eyes will be closed, and they do not get of out bed and walk around. As a result, RBD leaves sufferers and their bed partners at risk of injury due to the lashing or kicking motions associated with dreams of fighting or conflict.

As stated, muscle atonia is a hallmark of REM sleep, but in RBD the mechanisms that mediate muscle atonia in REM sleep are impaired. RBD is often seen in neurodegenerative disorders such as Lewy body dementia, Parkinson's disease and multiple system atrophy.[7] Less frequently, they have been described in multiple sclerosis, brainstem tumours and cerebrovascular disease. This is thought to be a result of disruption to the brainstem networks through which REM muscle atonia is generated. However, in otherwise healthy individuals, it has recently been recognised that RBD is part of the prodrome of these alpha-synucleinopathy neurodegenerative disorders, with estimates that as many as 90% of older patients with RBD convert to one of these diagnoses within 14 years of their diagnosis of RBD.[8] This fits with the current pathophysiological model of these diseases, whereby the pathological changes attributable to these conditions may affect the brainstem years or even decades before these conditions manifest in their typical phenotype.

In younger individuals, RBD can be associated with narcolepsy, and drugs like anti-depressants have been shown to precipitate RBD.[7] Treatment is usually supportive, encouraging withdrawal of any exacerbating medications, and prescribing melatonin or clonazepam in selected cases.

Other parasomnias arising from REM sleep include nightmare disorder, with frequent scary dreams resulting in awakening. This may be idiopathic, drug-related (for example, beta-blockers, levodopa), sleep deprivation-related, or secondary to psychiatric disorders (especially post-traumatic stress disorder). Sleep paralysis and hypnagogic hallucinations are also REM phenomena and may arise in isolation and not only within the context of narcolepsy (see section on 'Hypersomnias'). Many of these phenomena can be considered overlap sleep states, in that the brain may co-exist in different stages of sleep and wakefulness, with sleep paralysis representing the persistence of REM muscle atonia into wake, and hypnagogic hallucinations being considered the bleeding of dream imagery or mentation into wakefulness.

Similarly, other parasomnias arising from non-REM sleep may also be considered examples of the brain exhibiting more than one state of wake or sleep simultaneously. A range of behaviours may arise from non-REM sleep, typically deep N3 sleep. These phenomena are so common in childhood as to be considered part of normal brain development, but also persist in 1–2% of adults. The most widely recognised is sleep-walking, but non-REM parasomnias also encompass a range of other behaviours including sleep-talking, night terrors, confusional arousals, sleep-eating and sexsomnia (sexual behaviours in sleep). These conditions, in particular non-REM parasomnias associated with violent or sexual behaviour, have potential forensic implications, especially for males.

The behaviours associated with parasomnias arise due to arousal from deep slow wave sleep, with resultant dissociation of sleep states in different parts of the brain. Neurophysiological and imaging studies have shown that in susceptible individuals, arousal can result in persistent slow-wave sleep in frontal and hippocampal regions (resulting in disinhibition and failure of rational thinking), with waking rhythms or activity predominantly in motor and limbic regions (causing movement and strong emotions).[9,10] This susceptibility is likely to have a genetic basis, and there is often a family history, but any disruption of sleep by intrinsic factors such as sleep apnoea or anxiety, or extrinsic factors like noise or alcohol, may precipitate events. Sleep deprivation is often a priming factor, since it deepens N3 sleep and makes partial arousal more likely.

In contrast to RBD, there is no strong association between non-REM parasomnias and other neurological disorders. The treatment for non-REM parasomnias is largely focused on improving sleep quality through good sleep hygiene, improving sleep deprivation, treatment of triggering sleep pathologies, ensuring a safe sleeping environment, and avoidance of external triggers like alcohol. Coexisting psychiatric conditions should also be addressed. The mainstay of pharmacological therapy is clonazepam, although other options include melatonin, and antidepressants.

Hypersomnias

The differential diagnosis for someone who has excessive daytime sleepiness or a long sleep duration is extremely broad, and the majority of these patients will have an explanation other than a primary sleep disorder. These

differentials include insufficient sleep syndrome, which affects 1 in 5 of the adult population; the prescription or illicit use of sedating agents such as anti-neuropathic agents, opioids, sedating tricyclics or antiepileptic drugs, and psychiatric disorders. In particular, depression is considered to have early-morning waking as one of its cardinal biological features, but a subgroup of patients with major depressive disorder experience significant daytime sleepiness, both subjectively and on objective measures.

Narcolepsy

Narcolepsy is the archetypal hypersomnia.[11] It is not rare in neurological terms, affecting roughly 1 in 2000 people with peak age of onset in mid-teens and mid-thirties, and is an irreversible lifelong condition. The disorder is characterised by a failure to achieve stable sleep and wakefulness, as well as an instability of transitioning from non-REM to REM sleep.

Narcolepsy is typified by a tetrad of features, of which daytime sleepiness is the only mandatory criterion. This can range from a persistent tendency to doze off or fall asleep in unstimulating circumstances to irresistible sleep attacks that can occur even when highly stimulated. Other features of the classic tetrad relate to the inappropriate initiation or termination of REM sleep, with features of REM bleeding into wakefulness. These include sleep paralysis and hypnagogic hallucinations. Patients experience complete paralysis lasting seconds or minutes, often broken by an external stimulus or a small movement. Consciousness is fully preserved, and sleep paralysis can be terrifying, particularly if accompanied by hallucinations that typically take the form of figures or animals in the bedroom, or of the individual being pinned down by an external force, or out-of-body experiences.

Cataplexy, the final feature of the clinical tetrad, is a phenomenon that is almost pathognomonic of narcolepsy and, indeed, narcolepsy was previously defined as either with or without cataplexy. Cataplexy refers to the sudden loss of muscle tone in wakefulness, usually but not invariably triggered by strong emotion, particularly laughter or tone. It can result in complete collapse to the floor, but can also be segmental, only affecting the face, neck, or upper limbs. It is considered by some as representing the initiation of REM atonia inappropriately during wakefulness, although the pathophysiological mechanism of cataplexy is not fully understood.[11] Consciousness is fully preserved.

Narcolepsy is diagnosed through the exclusion of other disorders, a sleep study, and sometimes through the analysis of a peptide neurotransmitter called hypocretin in the cerebrospinal fluid (CSF). Almost all patients with cataplexy (termed narcolepsy type 1, or NT1) are deficient in CSF hypocretin, and this has led to the identification of the cause of narcolepsy. NT1 is thought to result from destruction of hypocretin-producing neurones in the lateral hypothalamus by an immune-mediated process. This nucleus is responsible for stabilising wakefulness and non-REM sleep. The vast majority of NT1 patients (>98%) are positive for the HLA DQB1*0602 allele (although roughly 25% of the normal population also carry this allele), and it is postulated that an environmental trigger – for example, H1N1 swine flu, vaccination, or upper respiratory tract infection – precipitates an immune response in genetically susceptible individuals.[11] Narcolepsy type 2 (NT2, defined as the absence of cataplexy or CSF hypocretin deficiency) remains less well defined, although it is recognised that some patients with NT2 may progress to NT1.[12]

The management of narcolepsy depends on the clinical features. The mainstay of treatment are stimulant agents such as methylphenidate, modafinil and dexamfetamine, alongside planned naps of short duration, and optimisation of sleep hygiene. REM phenomena such as hallucinations, sleep paralysis and cataplexy often respond to REM-restricting agents such as certain antidepressants; for example, venlafaxine, fluoxetine and tricyclics. Other drugs such as sodium oxybate and pitolisant may also be utilised in more specialist centres.

Restless legs syndrome and periodic limb movement disorder

There are other more common causes of hypersomnia. RLS is a very common sensorimotor disorder, affecting between 5–10% of the adult population, with prevalence increasing with age, and roughly twice as common in women as men.[13] It is characterised by four mandatory diagnostic criteria:

- The urge to move a body part, usually the legs, often associated with unpleasant sensations
- The urge to move is relieved by mobility, either completely or transiently/partially
- Immobility makes the urge to move worse
- The urge to move is under circadian influence and is worse in the evening and at night.

Restless legs syndrome is associated in the vast majority (~80–90%) of individuals with periodic limb movements of sleep (PLMS), which is defined as recurrent kicks or twitches of the legs. In some individuals these PLMS can give rise to disruption of sleep, and when there are clinical consequences from these PLMS they are defined as periodic limb movement disorder (PLMD). However, PLMS are very common, affecting about 50% of patients over 65 years old, and only about half of patients with PLMS have symptoms of RLS. RLS/PLMD can also present in a variety of ways. Patients may simply complain of the sensorimotor symptoms, but these may give rise to significant insomnia, or if sleep is very disrupted by PLMS, as hypersomnia with excessive daytime sleepiness and unrefreshing sleep despite long sleep duration.

Restless legs syndrome and PLMD have a significant overlap and have

shared underlying pathophysiology and genetic mechanisms. It is hypothesised that these conditions result from dopaminergic dysregulation in descending hypothalamic projections to the spinal cord.[14] They are primarily viewed as genetic, and a high proportion of patients report a positive family history, but RLS/PLMD is frequently secondary to iron deficiency, uraemia or pregnancy. RLS is also associated with a wide range of neurological conditions such as neuropathies and Parkinson's disease.

In most countries, the licensed treatments for RLS are primarily dopamine receptor agonists. In the long term, this class of drugs can potentially drive the condition to worsen, a phenomenon known as augmentation, especially if given at high doses. Maintaining brain iron levels (a proxy marker of brain iron stores is the serum ferritin, which should be maintained above 75mcg/L), and avoidance of dose escalation may mitigate this effect. Other classes of drugs used in RLS/PLMD include the alpha-2-delta ligands, opioids and clonazepam.

Obstructive sleep apnoea

Even more prevalent than RLS is OSA, which refers to the recurrent collapse of the airway in sleep associated with snoring, resulting either in partial airway obstruction associated with oxygen desaturations (hypopnoeas), or complete obstruction (apnoeas).[15] When occurring in conjunction with symptoms such as excessive daytime sleepiness, cognitive dysfunction, disrupted night-time sleep or nocturia, OSA is defined as OSA syndrome (OSAS). There remains some uncertainty as to the significance of OSA in the absence of any symptoms. It is often associated with obesity and neck circumference, but a normal BMI does not exclude OSAS and it may also be related to retrognathia or other anatomical abnormalities of the airway.

Obstructive sleep apnoea syndrome is of great relevance to most clinicians. It is one of the commonest causes of excessive daytime sleepiness, with some estimates of prevalence as high as 50% of adult males and 23% of females for moderate sleep apnoea (increasing due to changes in obesity rates worldwide).[16] OSAS increases the risk of diabetes mellitus, hypertension, hypercholesterolaemia and cardiac arrhythmias, and is therefore a risk factor for cardiovascular and cerebrovascular disease. Patients with OSAS may also present with cognitive dysfunction, headache, or mood disturbance. OSAS is also associated with erectile dysfunction, and there is increasing evidence on the association between OSAS and mild cognitive impairment/Alzheimer's disease.[17]

The management of OSAS includes weight loss, the use of mandibular advancement devices to cause protrusion of the lower jaw in sleep, or pneumatic splinting of the airway through the use of continuous positive airway pressure. Rarely, surgery to the upper airway may be considered.

Conclusions

Given that we spend a third of our lives asleep, it is perhaps of no surprise that disorders of sleep also influence almost every aspect of our waking lives. More surprising is the lack of education surrounding sleep disorders within the medical profession and, while this is gradually changing, there remains much progress to be made.

A basic understanding of the range of sleep disorders affecting all our patients makes the identification of a potential sleep disorder more likely. It can also result in the diagnosis and treatment of potential risk factors for a broad range of other medical conditions.

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