Narcolepsy: a clinical review

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▶ A video of cataplexy is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/practneurol-2014-000837).

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ABSTRACT

Despite the classic tetrad of clinical features that typify it, narcolepsy remains much under-diagnosed, in part, because of the wide spectrum of clinical phenotypes, but also because of its insidious onset, usually in a young person. The median time to diagnosis from first symptoms remains very long, around 10 years in the UK. Conversely, in the specialist setting, it is likely over-diagnosed, largely because of failure to exclude other causes of hypersomnia. There is an over-reliance on a biological marker of the condition, the multiple sleep latency test (MSLT), which, like many tests, has a significant false-positive and false-negative rate. This review aims to discuss some of the difficulties in achieving a diagnosis, interpretation of investigations, differential diagnosis, and appropriate management of patients with narcolepsy.

PATHOPHYSIOLOGY

Despite being described in the 17th century, the term 'narcolepsy', that is, to be seized by sleep, was only coined at the end of the 19th century. The symptom tetrad that we now associate with narcolepsy—excessive daytime sleepiness, hypnogogic hallucinations, sleep paralysis and cataplexy—was only described in 1957.[1] Three years later, Vogel[2] reported the association of narcolepsy with sleep-onset rapid eye movement periods (SOREMP), the basis of the multiple sleep latency test (MSLT).

Since then, our understanding of narcolepsy as a clinical and pathophysiological entity has dramatically moved forward, through immunological and genetic advances.

A strong genetic component is indicated by familial studies that show the risk of developing narcolepsy with cataplexy in a first-degree relative is 1–2%, a relative risk of 10–40.[3] There is a strong human leucocyte antigen (HLA) association, especially with the HLA DQB1*0602 haplotype. Up to 98% of patients with narcolepsy with cataplexy have this haplotype, compared to 25% of the general population. However, concordance rates in monozygotic twins are relatively low, suggesting an important role for environmental factors. The association with HLA haplotype and subsequent identification of an association with polymorphisms in the T-cell receptor locus in whole-genome association studies imply an autoimmune role in pathophysiology. There are suggestions of infective triggers: the strong seasonal variation in incidence of narcolepsy in China[4] suggests a role for winter infections, and patients with recent onset narcolepsy have high serum titres of anti-streptolysin O antibodies.[5] More recently, the H1N1 swine flu virus and/or vaccination has been linked to narcolepsy (see below). The search for antibodies mediating an immune response has not given consistent findings, although recent attention has focussed on the anti-Tribbles 2 analogue antibody.[6]

The identification of narcolepsy with cataplexy in dogs in the 1970s led to the discovery of mutations in the hypocretin-2 receptor gene through positional cloning,[7] and first implicated the role of hypocretin (also known as orexin) transmission in the pathogenesis of narcolepsy. Two closely related peptides, hypocretin-1 and hypocretin-2 occur only within the lateral hypothalamus: patients with narcolepsy with cataplexy show a loss of some or all of the 70 000 hypocretin-producing neurones in the lateral hypothalamus.[8] Low or absent cerebrospinal fluid (CSF) hypocretin-1 levels are consistently found in patients with narcolepsy with cataplexy, although this association is less strong with patients without cataplexy. Studies in humans have not identified mutations in hypocretin-receptor genes underlying narcolepsy, although one person with early onset narcolepsy with cataplexy had a mutation in the hypocretin peptide gene.[9] The hypothesis in humans is that there is a genetic predisposition to

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autoimmune attack on the hypocretin-producing neurones in the lateral hypothalamus, triggered by environmental factors, such as infective agents.

A full discussion of the neuroanatomical basis of narcolepsy is beyond the scope of this review, and is detailed elsewhere.[10] However, the hypocretin-producing locus in the lateral hypothalamus projects widely throughout the brain. Neuronal activity in this locus is highest in wakefulness, and is lower in sleep, particularly rapid eye movement (REM) sleep. Hypocretin-producing neurones stimulate histaminergic neurones in the tuberomamillary nucleus, noradrenergic neurones in the locus coeruleus, serotonergic neurones in the raphe nuclei and cholinergic neurones in the basal forebrain, all of which act to increase arousal state and activate the cerebral cortex. The hypocretinergic neurones also have excitatory projections to REM-off neurones in the ventrolateral periaqueductal grey and the lateral pontine tegmentum, thus stabilising non-REM sleep. Therefore, loss of these hypocretinergic neurones causes inherent instability in the neural network responsible for maintaining wakefulness and preventing REM sleep.

CLINICAL FEATURES

Narcolepsy affects approximately 1 in 3000 people, although the prevalence varies widely in different geographical regions, again implying a strong genetic influence. The age of onset ranges from early childhood to the fifth decade, but there is a bimodal distribution, with peaks of onset between 15 and 36 years of age.[11]

The hallmark of narcolepsy is instability of the transition of sleep and wake, as well as the transition between REM and non-REM sleep. This is the basis for features of the symptom tetrad. Only 10–15% of patients have all four symptoms. The only mandatory feature is excessive daytime sleepiness (Box 1), which should be present on an almost daily basis for at least 3 months, to fulfil the diagnostic criteria for narcolepsy.[12] Excessive daytime sleepiness can present as frank sleep attacks, but may be more subtle, such as constant sleepiness with occasional exacerbations. It is usually the first manifestation of narcolepsy. Typically, patients fall asleep for seconds or minutes, and find these brief naps refreshing. This is in contrast to individuals with other sleep disorders; patients with idiopathic hypersomnia tend to sleep for hours and feel unrefreshed on waking. Dreaming in short naps is another feature of narcolepsy, and represents inappropriately early REM sleep. Sleep attacks while standing, eating, or during physical exercise particularly suggest narcolepsy, but are not diagnostic; we have seen patients with severe sleep apnoea present with sleep attacks while standing in stimulating situations. Patients with narcolepsy have a total sleep time per 24 hour period that is normal or only slightly increased. Indeed, nocturnal insomnia, particularly sleep-maintenance insomnia, is another common feature of the condition (figure 1). Patients often wake at night feeling extremely refreshed and unable to return to sleep. This can result in the daytime sleepiness being blamed on poor sleep hygiene rather than narcolepsy.

Hypnogogic hallucinations affect 30–60% of patients. These may occur at sleep onset or sleep offset, and can be bizarre and frightening. They are

Box 1 International Classification of Sleep Disorders 2nd edition (ICSD-2). Diagnostic criteria for narcolepsy

Narcolepsy with cataplexy

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months.
B. There is a definite history of cataplexy, defined as sudden and transient episodes of loss of motor tone triggered by emotions. Note: to be labelled as cataplexy, these episodes must be triggered by strong emotions—most reliably laughing or joking—and must be generally bilateral and brief (<2 min). Consciousness is preserved, at least at the beginning of the episode. Observed cataplexy with transient reversible loss of deep tendon reflexes is a very strong, but rare, diagnostic finding.
C. The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by a multiple sleep latency test (MSLT); the mean sleep latency on MSLT is ≤8 min with two or more sleep-onset rapid eye movement periods (SOREMPs) following sufficient nocturnal sleep (minimum 6 h) during the night before the test. Alternatively, hypocretin-1 levels in the CSF are ≤110 pg/mL or one-third of mean normal control values.
D. The hypersomnia is not better explained by another sleep disorder or neurological disorder, mental disorder, medication use, or substance use disorder.

Narcolepsy without cataplexy

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months.
B. Typical cataplexy is not present, although there may be doubtful or atypical cataplexy-like episodes.
C. The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed by a MSLT. In narcolepsy without cataplexy, the mean sleep latency on MSLT is ≤8 min, with two or more SOREMPs following sufficient nocturnal sleep (minimum 6 h) during the night before the test.
D. The hypersomnia is not better explained by another sleep disorder or neurological disorder, mental disorder, medication use, or substance use disorder.

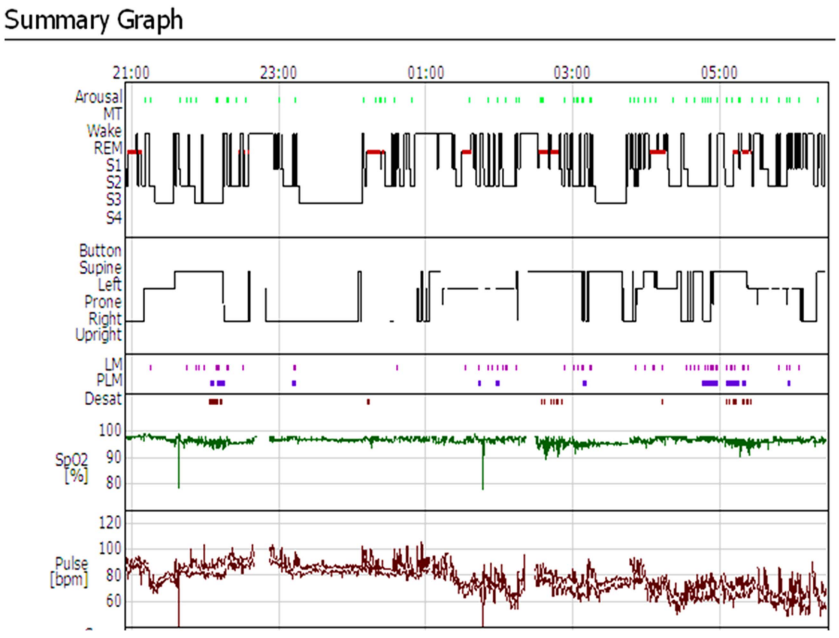

Figure 1 The polysomnogram shows characteristic features of narcolepsy, with very early onset of REM, within of few minutes of sleep onset, marked sleep fragmentation, and REM instability. There is little significant sleep-disordered breathing or periodic limb movements of sleep to explain the sleep fragmentation or excessive daytime sleepiness.

usually visual, although may be auditory or sensory. Occasional patients have spiritual or other unusual hallucinations, such as out-of-body experiences, describing themselves as floating above their sleeping selves; rarely, they find these comforting and want to avoid ending these experiences with medication.

Hallucinations can accompany sleep paralysis, which is especially frightening (figure 2). This can result in experiences of being physically or sexually assaulted, causing significant anxieties surrounding sleep. Sleep paralysis, which affects 25–50%, can be partial or complete, and occurs in full consciousness. Despite sparing

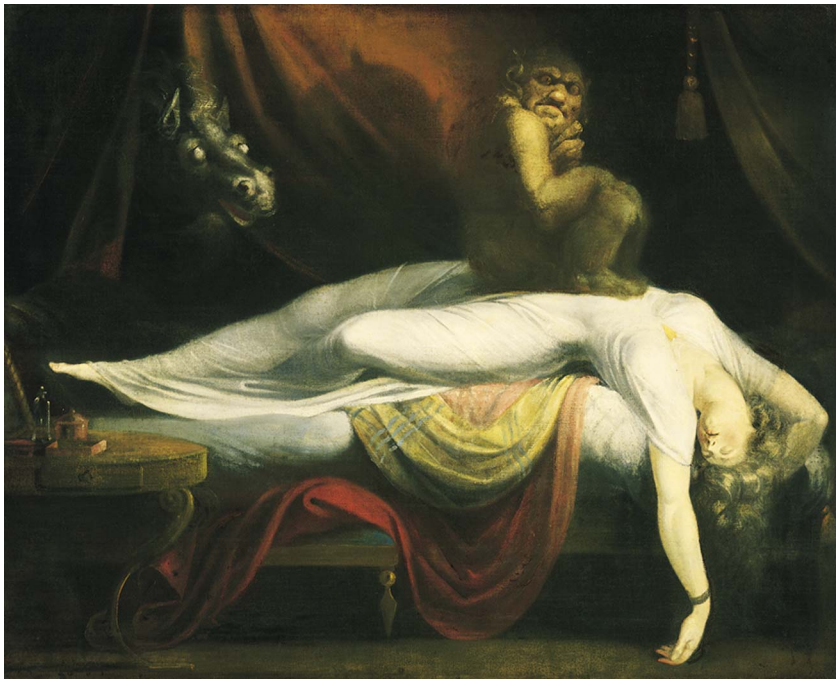

Figure 2 Henry Fuseli (1741–1825) The Nightmare, 1781; oil on canvas, 101.6 cm×127 cm, Detroit Institute of Arts. The painting illustrates hypnagogic hallucinations of the horse's head but also of the 'incubus', a demon pinning down the sufferer, commonly associated with sleep paralysis. Sleep paralysis is frequently associated with sensations of a heavy weight on the chest, and dyspnoea, thought to relate to the atonia of accessory breathing muscles in REM sleep.

diaphragmatic function, patients sometimes report shortness of breath or asphyxiation, contributing further to the terrifying nature of these events.

Hypnogogic hallucinations and sleep paralysis at sleep onset suggest narcolepsy: normal people can experience these, but usually at sleep offset.

The final feature of the classical tetrad is cataplexy, which usually develops within 3–5 years of onset of daytime sleepiness (it can occur up to 45 years later), but rarely precedes it.[13] Its presence defines a more homogeneous group of patients, on a clinical and pathophysiological level. Cataplexy describes the transient and sudden loss of muscle tone in full consciousness, usually precipitated by strong emotion or occasionally spontaneously; it occurs in 60–70% of patients. Loss of awareness/consciousness points strongly away from cataplexy, although it raises the possibility of loss of tone related to sleep attacks. It may be complete, affecting all muscles—apart from the diaphragm and the extraocular muscles—or may be segmental, affecting only the limbs, face or muscles affecting speech (see online supplementary video, provided courtesy of Prof Matthew Walker). Patients sometimes perceive unilateral weakness. Younger patients, in particular, often describe facial cataplexy in terms of embarrassment—they are extremely self-conscious that if they laugh in front of their friends, their facial slackening looks very odd. The onset is usually abrupt, although may wax and wane, and muscle tone returns to normal immediately when the attack ceases. Patients often can control or resist an attack. Cataplexy typically lasts seconds or minutes, although occasionally may be more prolonged, especially following sudden withdrawal of anticataplectic agents—'status cataplecticus'. When prolonged, there may be dream mentation and hallucinations. Cataplexy may also be associated with positive motor phenomena such as twitching of the face or limbs. Urinary incontinence can rarely accompany cataplectic attacks. Deep tendon reflexes are diminished or absent in cataplexy—a useful confirmatory clinic or bedside test. The neurophysiological correlate, the H reflex, is also altered, but normal subjects have similar H reflex changes during laughter, suggesting that cataplexy reflects an exaggerated normal mechanism.[14] Rather unhelpfully though, cataplexy usually requires some relaxation, and so, patients seldom develop cataplexy in the clinic.

With no gold standard test for narcolepsy, cataplexy has been considered pathognomic for the condition, but this should be interpreted with care. People will often describe 'going weak at the knees' with laughter, and cataplexy-like events can occur in normal people and those with other sleep disorders. Sagging of the jaw, falling to the ground and triggering by surprise or tickling are all help to indicate true cataplexy; although laughter is the most common trigger, it is less specific to cataplexy.

Cataplexy-like attacks can occur outside the context of narcolepsy:

- Niemann–Pick type C. About 10% of patients will have cataplexy; indeed, it may be its presenting feature.[15]
- Hyperekplexia represents an exaggerated startle response, and is usually caused by mutations in inhibitory glycine receptor genes.[16] It is associated with neonatal rigidity and generalised rigidity after startle; laughter does not precipitate this.
- Coffin–Lowry syndrome, a rare X-linked dominant disorder characterised by mental retardation, dysmorphic facies and skeletal abnormalities, may manifest as stimulus-induced drop episodes (SIDE). These drop events may have features of cataplexy or hyperekplexia.[17]
- Pseudocataplexy is a well recognised functional movement disorder.[18]

Patients with narcolepsy frequently have other features. In the elderly, REM sleep behaviour disorder is frequently a harbinger of idiopathic Parkinson's disease or of dementia with Lewy bodies, while in the young it is sometimes associated with narcolepsy.[19] Patients frequently report very vivid or even lucid dreaming. They may also show automatic behaviour, although this is a more general feature of sleep disorders. Occasionally, these may be mistaken for epileptic seizures. Cognitive dysfunction is another frequent problem, but this is probably due to the brain allocating resources to monitoring and to maintaining vigilance.[20] Depression and anxiety disorders are common,[21] although it is unclear if these result from the chronic condition, or are primary features of narcolepsy. Anosmia is also associated with narcolepsy.[22]

Patients may have an increased frequency of periodic limb movement disorder and obstructive sleep apnoea affecting sleep quality. Periodic limb movement disorder may be associated with weight gain, particularly in patients with cataplexy.[23] Weight gain appears unrelated to altered ghrelin or leptin levels.[24]

SYMPTOMATIC NARCOLEPSY

Narcolepsy may rarely result from other brain pathology, especially hypothalamic disease.[25] Symptomatic narcolepsy may develop in multiple sclerosis, head trauma, hypothalamic tumour, vascular lesions, neuromyelitis optica, acute disseminated encephalomyelitis, and other forms of brainstem encephalitis. Narcolepsy associated with psychotic features may occur with anti-N-methyl-D-aspartate (NMDA) antibodies, with and without frank clinical features of an encephalitis,[26] and is well described following von Economo's encephalitis. Inherited disorders, such as Niemann–Pick type C, Prader–Willi syndrome, myotonic dystrophy and epileptic encephalopathies comprise the most common causes of secondary narcolepsy. It may also develop with Wernicke's encephalopathy.

A narcolepsy-like picture may also occur in idiopathic Parkinson's disease, each having common

features such as anosmia and REM sleep behaviour disorder. Generally these patients are not hypocretin-deficient, and the symptoms perhaps reflect more diffuse brainstem dysfunction.[27]

Clinicians should note that symptomatic narcolepsy is rare, and current practice within our unit is not to scan patients unless there is clinical evidence of other neurological features, or if the phenotype is unusual, for example, isolated cataplexy.

DIFFERENTIAL DIAGNOSIS

Chameleons

Narcolepsy is often mistaken for other conditions, such as chronic sleep restriction, attention-deficit hyperactivity disorder, chronic fatigue syndrome and a range of psychiatric conditions such as atypical depression and psychotic illness, particularly if there are very prominent hypnagogic hallucinations or affective symptoms.

Mimics

A range of sleep disorders can simulate narcolepsy, particularly if occurring without cataplexy. These include obstructive sleep apnoea, restless legs syndrome/periodic limb movement disorder, idiopathic hypersomnia, sleep phase disorders and behaviourally induced inadequate sleep syndrome. The presence of cataplexy obviously helps to rule out many of these possibilities, but clinicians must ensure that the patient is describing true cataplexy rather than cataplexy-like episodes or pseudo-cataplexy. Behaviourally induced inadequate sleep syndrome affects 20–30% of adults; it is a very important diagnosis to exclude before making a diagnosis of narcolepsy without cataplexy. In practice, this can be very difficult, although the MSLT can sometimes help (see below). Patients with suspected chronic sleep deprivation should receive sleep hygiene advice, told to extend their sleep opportunity, and subsequently be reviewed. Actigraphy may help to confirm sleep duration before diagnostic testing; however, it may simply show 'behavioural' sleep rather than true 'neurophysiological' sleep. Patients with functional disorders may need prolonged home or inpatient telemetry to show discordance between true sleep and reported sleep duration. A long sleep time suggests idiopathic hypersomnia, as do prolonged daytime naps that last hours rather than minutes. Pharmacologically induced sleepiness is another common mimic. It is worth trying to withdraw sedating medication before diagnosing narcolepsy, though in practice this can be difficult. Depression may be associated with hypersomnolence and a shortened REM latency, and is another potential mimic.

In the specialist setting, there may be a tendency to over-diagnose narcolepsy—especially narcolepsy without cataplexy—as there is a view that stimulant therapy will treat the excessive daytime sleepiness, regardless of the underlying cause. However, diagnostic certainty needs to be as rigorous in narcolepsy as in other neurological conditions, for example, epilepsy, since narcolepsy is a life-long condition, usually requiring life-long treatment, and has physical, psychological and social consequences.

DIAGNOSTIC TESTING

The MSLT is the major diagnostic test for narcolepsy. According to the ISCD-2 criteria, a mean sleep latency of ≤8 min with REM sleep in at least two naps is diagnostic of narcolepsy, provided other conditions have been excluded. The MSLT gives the opportunity to fall asleep on four or five occasions at 2-hourly intervals over a day, with the patient monitored with EEG for sleep-staging purposes. The MSLT should always be performed after full polysomnography, to exclude other sleep disorders and to ensure adequate sleep on the night before—patients need a minimum total sleep time of 6 h for MSLT results to be valid. The patient should keep an adequate sleep diary, or should have actigraphy for 2 weeks before, to exclude significant sleep restriction, and should also have been off all drugs that might influence the results of the MSLT for 2 weeks. Sedating drugs obviously may shorten the mean sleep latency, and antidepressants or antipsychotics may REM-restrict patients, preventing sleep onset REM. Importantly, very recent withdrawal of these classes of drugs may cause REM rebound during the MSLT, generating sleep-onset REM.

The MSLT is a biological test with a high false-positive and false-negative rate. Among normal people, 6% of males and 1.5% of females have an MSLT that is diagnostic of narcolepsy.[28] Furthermore, 6% of patients with sleep-disordered breathing and 4% of patients with other sleep disorders have a positive MSLT.[29] An MSLT diagnostic of narcolepsy is not uncommon in behaviourally induced inadequate sleep syndrome. Conversely, patients with narcolepsy may have a normal MSLT before the subsequent diagnosis. I have one patient with two entirely normal MSLTs who has narcolepsy with cataplexy, and who is completely deficient in CSF hypocretin-1. Therefore, it is crucial to interpret the MSLT in the context of the clinical picture, much as the EEG is in the epilepsy clinic setting. If there is high clinical suspicion, then the MSLT should be repeated. Nevertheless, there are additional features of the polysomnography and MSLT that make narcolepsy more likely, such as REM sleep arising from wake or stage 1 non-REM sleep in the first REM period of the night, or in the daytime naps.[30 31]

Despite its limitations, the MSLT is mandatory to diagnose narcolepsy without cataplexy, and should be performed, if available, in patients with suspected narcolepsy with cataplexy.

More recently, there has been attention on measuring CSF hypocretin-1 levels as part of the diagnostic workup.[32] Approximately 90% of patients with narcolepsy and typical cataplexy have undetectable or low (defined as ≤110 pg/mL) levels of CSF hypocretin-1. This rate is much lower in patients without cataplexy, at 20–30%. Therefore, a low CSF hypocretin-1 confirms the diagnosis of narcolepsy with or without cataplexy, but a normal CSF hypocretin-1 does not help in diagnosing narcolepsy without cataplexy. In practice, CSF hypocretin-1 levels are not often tested, and are most useful in confirming a diagnosis of narcolepsy in someone with atypical features, or for confirming the clinical impression that a patient with apparent narcolepsy with cataplexy has an alternative diagnosis. However, proposed changes to the diagnostic criteria for narcolepsy in the forthcoming third edition of ICSD include the division of narcolepsy into those with cataplexy and/or low or deficient CSF hypocretin-1 levels, and those without cataplexy and normal hypocretin-1. This change in the definition of subtypes to include a laboratory investigation implies that many of those without cataplexy, but abnormal hypocretin, will go on to develop cataplexy later in the disease course.

Historically, HLA typing has been part of the diagnostic work-up. By contrast with hypocretin, it is tested for on a venous blood sample. However, HLA typing has very limited clinical use. The DQB1*0602 haplotype occurs in approximately 95% of patients with narcolepsy with cataplexy, but only 40–60% of people without cataplexy. Moreover, this haplotype is common in the general population (20–25%). Therefore, its positive predictive value is poor except for those with cataplexy, in whom a positive test is no more useful than a history of typical cataplexy. However, 98% of patients with a low CSF hypocretin-1 are DQB1*0602 positive, and so testing for the haplotype may help in those with atypical cataplexy where a lumbar puncture is being considered; if the patient is negative for the haplotype then the CSF hypocretin-1 is likely to be normal.

MANAGEMENT

The first intervention for anyone with a sleep disorder is appropriate sleep hygiene advice. This is equally appropriate for patients with narcolepsy or suspected narcolepsy, to ensure adequate sleep opportunity to rule out an element of chronic sleep deprivation, but also to help control symptoms of excessive daytime sleepiness. Some patients prefer to manage their symptoms without medication, and if lifestyle permits, planned naps can be sufficient to establish reasonable control in some patients. It is generally recommended to limit daytime naps to 15 min or so, as longer naps risk entering non-REM stage 3 sleep, potentially inducing grogginess or sleep inertia, and with possible deleterious consequences on night-time sleep.

For most patients, however, stimulant medication is the mainstay of treatment (see online supplementary table S1). Modafinil and dexamphetamine are licensed agents, but methylphenidate is also commonly prescribed. Modafinil is the best tolerated of these, with a good safety profile, but unlike the others, is not significantly anticataplectic. Like other stimulants, it increases monoamine release, but also elevates hypothalamic histamine levels, and is considered a 'wake-promoter' rather than an amphetamine-like stimulant.[33] It has a low risk of addiction. Common side effects include headache, anxiety, palpitation and rarely, hypertension. Its safety profile is extremely good, but there are concerns regarding drug rash in children. The starting dose is usually 100 mg in the morning, increasing up to 200 mg after a few days. It can be further increased with a second dose at lunchtime, to avoid causing sleep initiation difficulties, with a maximum licensed dose of 400 mg per day; occasionally patients need higher doses. The duration of action is relatively long, with an elimination half-life of 10–15 h.

Methylphenidate and dexamphetamine are amphetamines with a higher rate of adverse events, especially hypertension and psychiatric effects. They should be used very cautiously in people with a cardiac history. Despite these concerns, these drugs have not been associated with increased serious cardiac events or death, at least in young and middle-aged adults.[34] Dexamphetamine is typically started at a dose of 5 mg twice daily, with a maximum daily dose of 60 mg. Its duration of action is relatively long, around 6–10 h. Because of the short duration of action of methylphenidate, approximately 3–4 h, my preference is a single morning dose of a sustained-release preparation, occasionally with a much smaller dose of normal release methylphenidate to overcome morning sleep inertia or postlunch sleepiness. Modafinil can be used in combination with either of the amphetamines if daytime sleepiness remains problematic. All these stimulants may impact on the efficacy of hormonal contraception, yet pregnancy should probably be avoided on these drugs, although this is not always practical.

Habituation to stimulant agents does sometimes occur. Switching between different drugs regularly can be effective, as can drug holidays.

Alternative agents for treating daytime sleepiness include selegiline, mazindol and nicotine. Many patients report a worsening of daytime sleepiness when giving up smoking, and I have one patient who controls her symptoms with nicotine lozenges. Indeed nicotine patches help sleep drunkenness on waking. Unfortunately, mazindol is currently very difficult to obtain due to European manufacturing problems. Atomoxetine is also beginning to be used in narcolepsy, although experience is very limited.

Habituation is not the only cause of apparent loss of control over daytime sleepiness. Patients

occasionally develop periodic limb movement disorder due to antidepressant drugs or sleep apnoea due to weight gain; clinicians should consider repeating sleep studies in patients who are losing control over their daytime sleepiness.

Although not a standard therapy, addressing night-time sleep may also help daytime symptoms. Treating other sleep pathologies also helps; for example, pregabalin may help coexisting periodic limb movement disorder as well as consolidating sleep and increasing the proportion of slow-wave sleep. Trazodone, Z drugs and other sedatives may also help in treating night-time insomnia.

Cataplexy may respond methylphenidate or dexamphetamine, but more usually requires specific anticataplectic agents. Clomipramine and venlafaxine are licensed for this indication, and the choice largely depends on other features of narcolepsy. Clomipramine at night may help if there is prominent night-time insomnia, and venlafaxine can provide an additional stimulant effect. Fluoxetine can also be very effective and is usually better tolerated than venlafaxine or clomipramine.

Sodium oxybate is a relatively new drug for treating cataplexy (licensed indication) and excessive daytime sleepiness. It is a $GABA_B$ agonist, although its mechanism of action is not entirely understood. It is taken as a liquid, and because it has a very short half-life, patients should take one dose immediately before bed, with a second dose 3–4 h later. Some patients wake spontaneously, but others require an alarm to wake them.

There are several issues specific to sodium oxybate. It is extremely expensive, costing approximately £10–12 k per annum, and in the UK, prescribing requires an independent funding request. Clinical commissioning groups almost invariably reject 'exceptional circumstances' funding requests, arguing that prescribing a drug licensed for a not particularly rare condition does not constitute exceptional circumstances. It is also potentially a drug of abuse, and is, therefore, a controlled drug. Because it is extremely sedating, it has been used criminally as a 'date-rape' drug. It also acts as a respiratory depressant and deaths have occurred in combination with alcohol or other central nervous system-depressant drugs. Despite these limitations, it is a widely used drug where funding is not an issue, and in the USA is often used as a first-line drug for narcolepsy with cataplexy. In the UK, it is more commonly used in patients with refractory cataplexy, or occasionally, refractory excessive daytime sleepiness in narcolepsy with cataplexy. Common side effects include gastrointestinal disturbance, hypertension, nocturnal enuresis, sleepwalking and, less commonly, depression and other psychiatric features. Patients are instructed not to mix it with alcohol at all: if they do consume alcohol, they should not take the sodium oxybate that night; the same applies for all sedatives. Sodium oxybate may exacerbate sleep-disordered breathing, so patients with sleep apnoea should have this adequately controlled. For those patients who tolerate it, it is usually very effective, although patients are rarely able to withdraw completely from all stimulants or other anticataplectic agents. We have trialled over 80 patients on sodium oxybate, approximately two-thirds of whom stay on it long-term.

One major issue with managing narcolepsy is that general practitioners may be uncomfortable with the prescribing of these drugs in the community. Because of the geographic areas that most sleep centres cover, prescribing from hospital can be problematic; shared care protocols can facilitate primary care involvement in management.

Experimental treatments include immunomodulatory therapy on the basis that, in the acute setting at least, suppression of the presumed immune-mediated attack on hypocretin-producing neurones may modify the disease course. Intravenous immunoglobulins within the first few weeks of onset in narcolepsy with cataplexy may produce persistent clinical improvements,[35] but not always.[36] At present, there is no clear evidence justifying its use.

Hypocretin agonists have also been proposed to treat narcolepsy.[37] Overexpression of hypocretin in genetically altered mice prevents the development of narcolepsy in hypocretin neurone-ablated mice, and intraventricular hypocretin maintains wakefulness and suppresses cataplexy. Unfortunately, to date, there has been no development of a hypocretin agonist small enough to cross the blood–brain barrier. Other potential novel therapies being explored include histamine antagonists and melanin-concentrating hormone receptor antagonists.[38]

NARCOLEPSY AND SWINE FLU

There has been recent attention on the reported association of narcolepsy with cataplexy with the Pandemrix H1N1 flu vaccine, approved by the European Medicines Agency in September 2009.[39] In August 2010, pharmacovigilance bodies in Scandinavia reported six cases of narcolepsy possibly related to Pandemrix; since then, several European studies have suggested a 14-fold risk of narcolepsy associated with this vaccine. All cases have been positive for the DQB1*0602 haplotype. This association appears robust, and appears unrelated to faster ascertainment of cases due to greater awareness. It is unclear if perhaps the H1N1 vaccine simply accelerated disease onset in those who were going to develop narcolepsy anyway. If so, one would expect to see a drop in new cases below baseline after the spike of 'triggered' cases was over. There may also be a link between H1N1 flu infection itself and narcolepsy, although the link is far less strong than that with the Pandemrix vaccination.

More recently, two hypocretin epitopes that bind DQB1*0602 have been shown to activate a subpopulation of CD4 T cells in narcolepsy patients but not DQB1*0602-positive normal controls.[40] Furthermore, vaccination of narcolepsy patients with a flu vaccine containing H1N1 epitopes caused an increase in hypocretin-reactive T cells, and in vitro H1N1 epitopes also show activation of this T-cell population, suggesting possible molecular mimicry of hypocretin by H1N1 epitopes. Perhaps the strong association with the Pandemrix vaccine relates to stronger stimulation of the T cell response due to the adjuvant used in the vaccine.

DRIVING AND NARCOLEPSY

All drivers, whether suffering from a sleep disorder or not, have a legal duty not to drive if excessively sleepy, and sleepiness is not an excuse for an accident in a court of law. However, once diagnosed with narcolepsy, patients have a legal duty to inform the driving licensing authorities that the diagnosis has been made and to cease driving. The UK Driver and Vehicle Licencing Agency (DVLA) guidance recently amended its guidance. Group 1 (ordinary) license holders require 3–6 months of 'satisfactory control of symptoms' with appropriate treatment. If they are not taking treatment, they need to show maintained wakefulness objectively, such as with the 'maintenance of wakefulness test' or the Osler's test, a rather tedious vigilance task. In practice, 'satisfactory control of symptoms' is a rather grey area, as patients may be sleepy when unstimulated but may have no problems maintaining alertness while driving. Our current policy is to undertake maintenance of wakefulness tests or Osler's test on patients with a significantly high Epworth Sleepiness Score. Cataplexy is a little easier, with the DVLA asking if there remains 'easily provoked' cataplexy. Group 2 (heavy goods) licence holders may have their licence reissued after a specialist sleep assessment and a satisfactory test of objective wakefulness.

CONCLUSIONS

Over the last three decades, our understanding of the pathophysiology of narcolepsy has leapt forward, and we now have an almost gold standard diagnostic test, CSF hypocretin-1, at least for the subgroup of narcolepsy in which cataplexy is present. However, it is for these patients that arguably a gold standard diagnostic test is less important, since there are clinical features that, if properly elicited, are themselves diagnostic. By contrast, narcolepsy without cataplexy remains an uncertain entity, and probably comprises a heterogeneous group, some with a *forme fruste* of narcolepsy with cataplexy, others misdiagnosed, and others perhaps with a still yet unidentified different central hypersomnia.

Narcolepsy remains a diagnosis of exclusion, and clinicians should explore alternative diagnoses. This mostly involves an adequate history; although diagnostic testing can help, clinicians should be aware of their limitations.

RESOURCES FOR PATIENTS

Narcolepsy UK
http://www.narcolepsy.org.uk
A UK-based patient support organisation, with online resources, forums and regular national meetings for patients with narcolepsy and their relatives.

Narcolepsy Network
http://www.narcolepsynetwork.org
A US-based national charity with a wide variety of online resources and links to other useful sites.

The Stanford Center for Narcolepsy
http://www.psychiatry.stanford.edu/narcolepsy
Helpful clinical resource, including movie clips of animal models and humans with cataplexy.

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