What respiratory physicians should know about narcolepsy and other hypersomnias

Stephen Klaus, Aoife Carolan, Deirdre O'Rourke and Barry Kennedy

Department of Sleep Medicine, St James's Hospital, Dublin, Ireland.

Corresponding author: Barry Kennedy (bkennedy@stjames.ie)

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Abstract

Narcolepsy and related central disorders of hypersomnolence may present to the sleep clinic with excessive daytime sleepiness. A strong clinical suspicion and awareness of the diagnostic clues, such as cataplexy, are essential to avoid unnecessary diagnostic delay. This review provides an overview of the epidemiology, pathophysiology, clinical features, diagnostic criteria and management of narcolepsy and related disorders, including idiopathic hypersomnia, Kleine–Levin syndrome (recurrent episodic hypersomnia) and secondary central disorders of hypersomnolence.

Educational aims

- To provide an overview of the diagnosis and management of narcolepsy.
- To compare with other central disorders of hypersomnolence, highlighting clinical and diagnostic differentiating factors.

Introduction

Narcolepsy is a chronic, disabling neurological disorder characterised by daytime sleepiness and recurrent episodes of muscle weakness (cataplexy). It is an under-recognised and under-diagnosed condition with a mean interval of up to 15 years between first presentation to medical care and diagnosis [1]. As narcolepsy is eminently treatable, it is important that clinicians recognise its manifestations promptly so delays in care are avoided.

Epidemiology

The prevalence of narcolepsy in Western populations lies between 0.02% and 0.05% [2, 3]. It is similar in Asia where prevalence has been measured at 0.015% in Korea and 0.034% in Hong Kong [4, 5]. Type 2 narcolepsy accounts for approximately one-third of cases [2].

The onset of narcolepsy has been associated with infection. The 2009 H1N1 influenza pandemic was associated with a three-fold increase in narcolepsy onset [6], while anti-streptolysin O titres are higher in individuals with narcolepsy within 3 years of onset compared to controls [7]. Disease onset also shows significant seasonal variation: Han *et al.* [6] showed that symptom onset was seven times more likely to occur in March than in November. These data suggest that the pathological process of narcolepsy may be triggered by an upper respiratory tract infection in winter leading to symptom onset in spring.

In August 2010, the Swedish Medical Agency reported a case series of patients who were diagnosed with narcolepsy after receiving the Pandemrix influenza A (H1N1) vaccine [8]. This vaccine had been adjuvanted with AS03. A subsequent report from Finland showed that children who received the

Pandemrix vaccine had a 12.7-fold increase in the incidence of narcolepsy compared to unvaccinated children [9]; reports from France, Norway, England and Ireland showed similar increases in the incidence of narcolepsy in both children and adults [10].

Of note, this increase in narcolepsy was not seen in populations vaccinated with other influenza A (H1N1) vaccines. As these other vaccines were unadjuvanted or adjuvanted with MF59, it was speculated that the AS03 adjuvant of the Pandemrix vaccine may be the culprit immunogen.

In Quebec, Canada, vaccination against H1N1 was performed with the Arepanrix vaccine. This was also adjuvanted with AS03. However, although an increase in incidence of narcolepsy was noted, it was not as high as that observed with the Pandemrix vaccine [11]. It is unclear why more cases were associated with Pandemrix than with Arepanrix. It may be related to differences in the genetic susceptibility of the two populations, in how the two vaccines were manufactured or in the relative composition of their viral proteins [12, 13].

Pathophysiology

Orexins (also known as hypocretin) are neurotransmitters that are synthesised in the lateral hypothalamus. They relay excitatory output from the hypothalamus to areas of the brain that mediate arousal, feeding and autonomic tone [14].

The absence of orexins in the central nervous system is a hallmark pathological finding of narcolepsy. In a canine model of narcolepsy, mutations in orexin receptors were identified in 17 dogs with narcolepsy and were absent in all 36 controls [15]. Furthermore, the brains of narcoleptic patients demonstrate large reductions in orexin neurons compared to controls [16, 17]. Finally, orexins have been shown to be absent from the cerebrospinal fluid (CSF) of patients with narcolepsy [18]. Other data indicate how orexin deficiency leads to inability to maintain wakefulness [19–22] and to the inability to suppress rapid eye movement (REM) sleep [23, 24].

The precise mechanism by which orexin-secreting neurons are destroyed in narcolepsy is unclear. Immunohistochemical analysis of the brains of narcoleptic patients show that cell loss in the hypothalamus is specific to orexin-secreting cells; neurons secreting melanin-concentrating hormone, which are intermixed with orexin-secreting neurons in the hypothalamus, were preserved in these patients [16]. This discrete targeting of orexin-secreting neurons indicates that the aetiology of narcolepsy is likely to be autoimmune, although this has not been proven definitively. Nevertheless, despite the lack of aetiological clarity, aberrant T- and B-cell function, human leukocyte antigen (HLA) expression, and genetic variation are known to feature in this immune response.

T-cells

Investigators have postulated that the destruction of orexin neurons is mediated by T-cells (figure 1) [14, 25]. In this model, major histocompatibility complex (MHC) class II molecules on antigen-presenting cells present foreign antigens (*i.e.* H1N1 virus or *Streptococcus*) to the T-cell receptor (TCR) of $CD4^+$ T-cells. In the presence of a co-stimulatory molecule, the $CD4^+$ cell is activated and secretes cytokines to eliminate the antigen. Memory T-cells are subsequently formed to fend off subsequent attacks by the antigen. It is postulated that in narcolepsy, orexin neurons display similar epitopes to the foreign antigens and thus become a target for destruction by memory T-cells.

Evidence for this model of T-cell-mediated destruction is found in the strong association between narcolepsy and the HLA allele DQB1*0602. This allele is found in 90% of patients with narcolepsy [26]; in fact, its expression increases risk of narcolepsy 200-fold [27].

B-cells

The highly specific targeting of the orexin-secreting neurons in the hypothalamus suggests the presence of an autoantibody that is directed against these neurons. Tribbles homolog 2 (TRIB2) has been shown to be elevated in the serum of patients with narcolepsy with cataplexy [28]; however, murine models investigating its role in the pathogenesis of narcolepsy show inconsistent results [29, 30]. Antibodies to orexin and its receptors were shown to be elevated in narcolepsy patients who had received the Pandemrix vaccine compared to non-narcoleptic patients who had been infected with 2009 influenza A (H1N1) or received another H1N1 vaccine [13]. However, other studies indicate that these antibodies only occur in a small minority of narcolepsy patients [31, 32]. In summary, investigators are yet to identify an antibody that is both injurious to orexin neurons and elevated in the serum or CSF of narcolepsy patients; as such, the role of antibodies in the pathogenesis of narcolepsy is yet to be completely understood.

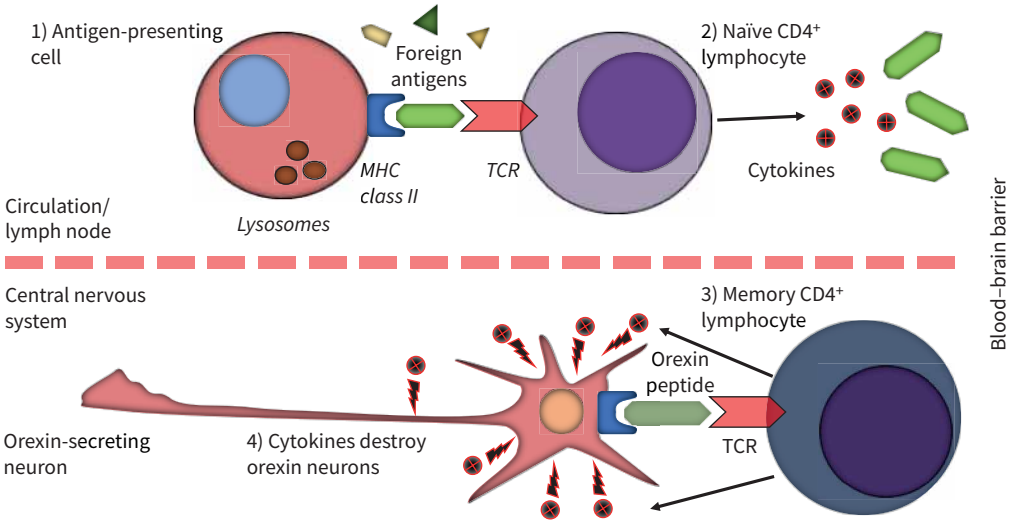

FIGURE 1 Putative model of T-cell-mediated destruction of orexin-secreting neurons. In this putative model, 1) antigen-presenting cells present foreign antigens (*i.e.* H1N1 or *Streptococcus*) to the T-cell receptor (TCR) of a $CD4^+$ T-lymphocyte *via* the major histocompatibility complex (MHC) class II molecule. 2) Naïve $CD4^+$ T-lymphocytes are activated and produce cytokines that eliminate the foreign antigen. 3) Following this infection, memory $CD4^+$ cells now circulate. 4) Orexin peptides display epitopes similar to those present on foreign antigens; memory $CD4^+$ T-cells, which have crossed the blood–brain barrier, recognise these epitopes and release cytokines that attack and damage orexin neurons. Italics indicate sites of genetic variation; variation in genes encoding cathepsin H (important in the overall degradation of lysosomal proteins), MHC class II molecules, TCR-α and TCR-β have been associated with narcolepsy.

Genetic variation

Variation in genes regulating immune peptides may also contribute to the pathogenesis of narcolepsy. Loci that have been associated with modulated disease risk include TCR-α, TCR-β, cathepsin H, tumour necrosis factor superfamily member 4, interferon receptor regions and purinergic receptors [33–35].

Clinical features

The onset of narcolepsy usually occurs in the second or third decade. Patients typically present with daytime sleepiness as well as features of REM sleep occurring during periods of wakefulness.

Daytime sleepiness is often the most troublesome symptom and leads to difficulties with school, work or driving. Paradoxically, patients with narcolepsy also complain of an inability to maintain sleep at night. In fact, when sleep is measured over a 24-h period, patients with narcolepsy sleep for the same amount as controls [36]. This indicates that the primary defect in narcolepsy is not so much excessive sleep as an inability to resist or maintain sleep. Severity of daytime sleepiness is usually assessed by the Epworth Sleepiness Scale (ESS).

REM sleep is manifest by vivid dreams, rapid eye movements and hypotonia of the non-respiratory skeletal muscles. Hallucinations, sleep paralysis and cataplexy are clinical manifestations of a “flux” state in which features of REM sleep intrude into the state of wakefulness [37].

Hallucinations can occur when patients are falling asleep (hypnagogic) or waking up (hypnopompic). They are often disconcerting and represent the vivid dreams of REM sleep occurring as a patient straddles wakefulness and sleep. Sleep paralysis occurs when the hypotonia of REM sleep persists after waking. It should be noted that both of these features can occur sporadically in the general population; nevertheless, recurrent events should raise suspicion for narcolepsy.

Cataplexy is the onset of REM-associated hypotonia occurring while the patient is awake. Its physical manifestations run a spectrum from facial droop to full body paralysis. Cataplexy is triggered by emotions such as surprise or laughter. It usually lasts for a few seconds but can continue for a few minutes, during which time the patient is fully conscious [14, 36].

Finally, patients with narcolepsy are also at risk of a range of comorbidities. They are liable to develop other sleep disorders such as REM sleep behaviour disorder, non-REM (NREM) parasomnias, periodic limb movements during sleep and obstructive sleep apnoea (OSA) [38–40]. Non-sleep disorders include obesity, diabetes, depression and cardiovascular disease [38, 41]. Some epidemiological data indicate an increased risk of all-cause mortality [42].

Investigation and diagnosis

The differential diagnosis of narcolepsy includes sleep deprivation, idiopathic hypersomnia, circadian phase disorders, periodic limb movements disorder (PLMD) and OSA [36]. While the presence of sleep paralysis, hallucinations and particularly cataplexy helps differentiate narcolepsy from other disorders, formal diagnostics are recommended before treatment is commenced.

The investigation of choice for narcolepsy is overnight polysomnography (PSG) followed by multiple sleep latency tests (MSLTs). The purpose of the PSG is to screen for the presence of other sleep disorders (*i.e.* OSA or PLMD) and to ensure that the patient has slept for at least 6 h before MSLTs.

MSLTs consist of four nap tests. Each test consists of a 20-min opportunity to fall asleep; each test is spaced 2 h apart. Mean sleep latency is the average time taken to fall asleep across all four naps. A narcoleptic patient will demonstrate a mean sleep latency of <8 min. Furthermore, at least two sleep-onset REM periods (SOREMPs) must be demonstrated over the course of the PSG and four nap tests. A SOREMP occurs when the patient enters REM sleep within 15 min of sleep onset [36, 43]. Of note, SOREMPs tend to arise from NREM stage 1 sleep in the presence of narcolepsy; conversely, SOREMPs associated with other sleep disorders (*e.g.* PLMD or inadequate sleep) tend to arise from NREM stage 2 sleep [44].

These criteria on sleep study have a sensitivity of 92% and a specificity of 96% for narcolepsy. Behaviourally induced insufficient sleep syndrome, shift work, OSA and cocaine withdrawal are causes of false positives; 2 weeks of wrist actigraphy are recommended prior to sleep tests to ensure adequate sleep is being obtained regularly. As many antidepressants suppress REM sleep, false negatives can be avoided by discontinuing these medications for at least 1 week prior to the study. A toxicology screen is also helpful [36, 43].

Magnetic resonance imaging of the brain should also be considered, as narcolepsy may, rarely, present secondary to head trauma, hypothalamic lesions or multiple sclerosis.

If diagnostic doubt persists after sleep studies, a lumbar puncture is recommended for measurement of orexin levels; this is particularly helpful in the context of cataplexy. In type 1 narcolepsy, orexins will be absent in the CSF [45].

The diagnosis of type 2 narcolepsy remains somewhat controversial. These patients present with daytime sleepiness but no cataplexy. Like type 1 narcolepsy, sleep studies show reduced mean sleep latency and at least two SOREMPs; CSF testing for orexins will be normal or intermediate. It is unclear whether this syndrome represents true narcolepsy or is a separate category of central hypersomnia [43].

Treatment

As orexin-secreting cells cannot be restored to the hypothalamus, a cure for narcolepsy is lacking. At present, the aims of treatment are symptom control and restoring quality of life. Ideally, treatment should take place in a specialist sleep centre with a multidisciplinary team consisting of doctors, clinical nurse specialists, sleep physiologists, pharmacists, dietitians and psychologists.

Non-pharmacological

Non-pharmacological modalities include optimising sleep hygiene, regular naps, balanced diet, distraction techniques and exercise [46]. They are a common feature of self-management in patients with narcolepsy and are used for both cataplexy and excessive daytime sleepiness (EDS) [47]. Daytime napping has been shown to improve performance testing and mean sleep latency [48, 49]. Of note, combining non-pharmacological modalities with stimulant medication may provide additional benefits in terms of severity of symptoms severity and mean duration of daytime sleep [50]. Finally, there is growing interest in the role of cognitive therapy in the treatment of narcolepsy. This aims to reduce maladaptive thoughts that occur in response to the psycho-social challenges associated with narcolepsy [51, 52].

Pharmacological

Pharmacological interventions target either daytime somnolence and/or symptoms of REM intrusion. It should be noted that there is a paucity of data comparing wakefulness-promoting agents; as such, there are multiple options for first-line therapy. The pharmacokinetics of these stimulant drugs are displayed in table 1.

Modafinil

Modafinil is a wakefulness-promoting agent that exerts its effect by augmenting dopamine transmission [53]. Randomised controlled trials (RCTs) demonstrate that modafinil improves the ESS score, MSLT results and maintenance of wakefulness test (MWT) results [61, 62]. Quality of life is also significantly increased [63]. Common side-effects include headache, nausea and anxiety. Clinically significant increases in blood pressure occur in <1% of patients [64]. A recent European guideline for the treatment of narcolepsy in adults recommends modafinil monotherapy as first-line treatment when EDS is the predominant symptom [65].

Armodafinil

Armodafinil is the R-enantiomer of modafinil. A multicentre, double-blind RCT showed that armodafinil improved MWT results and Clinical Global Impression of Change (CGI-C) scores. Like modafinil, the most common adverse events were headache, nausea and dizziness [66].

Solriamfetol

Solriamfetol also promotes wakefulness by inhibiting dopamine and noradrenaline re-uptake. It is a relatively new drug with little real-world clinical data at present. In a double-blind, placebo-controlled RCT, solriamfetol was associated with significant improvements in MWT, ESS and CGI-C scores. The most common adverse events were headache, nausea and reduced appetite [67, 68]. The recent European guideline recommends solriamfetol monotherapy as a first-line treatment when EDS is the predominant symptom [65].

Pitolisant

Pitolisant is a histamine H3 receptor antagonist/inverse agonist. It increases the concentration of histamine in the synaptic cleft, which in turn increases wakefulness [58]. Dauvilliers *et al.* [69] conducted a double-blind, parallel-group RCT that demonstrated that the effect of pitolisant on ESS scores was superior to placebo and non-inferior to modafinil. Szakacs *et al.* [70] reported in a double-blind RCT of 106 patients that pitolisant significantly reduced weekly cataplexy rate compared to placebo. There were more treatment-related adverse events in the pitolisant group compared to placebo. Guidelines recommend pitolisant as a first-line agent when EDS is the predominant symptom or when EDS occurs with mild to moderate cataplexy [65].

Methylphenidate and amphetamines

Methylphenidate is a short-acting stimulant that is thought to inhibit dopamine and noradrenaline re-uptake from the synaptic cleft [59]. Despite its widespread use, there is a paucity of data demonstrating its clinical efficacy in narcolepsy. In a controlled study of six patients with narcolepsy who received methylphenidate, treatment was associated with improvements in daytime sleepiness, ability to perform tasks and MWT results [71]. Insomnia and decreased appetite are the main adverse events associated with use. Underlying cardiac conditions and risk factors for psychosis are contra-indications to its use [72].

TABLE 1 Pharmacokinetics of wakefulness-promoting agents

	Absorption from GI tract	t_{max}, h	$t_{1/2}$, h	Elimination	Interaction with OCP
Modafinil [53, 54]	Rapid	2–4	12	Predominantly hepatic metabolism	Reduces efficacy
Armodafinil [55, 56]	Rapid	2–4	15	Predominantly hepatic metabolism	Reduces efficacy
Solriamfetol [57]	Rapid	2	6	Predominantly unchanged in urine	None
Pitolisant [58]	Rapid	3	12	Predominantly in urine	Reduces efficacy
Methylphenidate [59]	Rapid	3	2–3	Predominantly in urine	None
Sodium oxybate [60]	Rapid	<1	<1	Rapid hepatic metabolism	None

GI: gastrointestinal; t_{max}: time of maximum plasma concentration; $t_{1/2}$: elimination half-life; OCP: oral contraceptive pill.

Amphetamines such as amphetamine, methamphetamine and dextroamphetamine can also be considered if other wakefulness-promoting agents are ineffective. Side-effects include aggression, insomnia and irritability. Like methylphenidate, there is a paucity of data regarding their use in narcolepsy and they should be avoided in patients with cardiovascular and psychiatric illness [46].

Recent guidelines recommend methylphenidate or amphetamines as second-line treatment for EDS [65].

Venlafaxine and other antidepressants

Given their ability to suppress REM sleep, antidepressants are prescribed in narcolepsy to treat cataplexy as well as hallucinations and paralysis. Venlafaxine acts through selective inhibition of serotonin and noradrenaline and is the most prescribed antidepressant in narcolepsy. Its main side-effects include headache, dry mouth and nausea. Although its recommendation is based on expert opinion, European guidelines recommend its use as a first- or second-line agent for cataplexy [65]. Other antidepressants such as the selective serotonin reuptake inhibitor fluoxetine and the tricyclic agent clomipramine can also be considered [46].

Sodium oxybate

Sodium oxybate is a GABA (gamma-aminobutyric acid) receptor B agonist. It improves quality of nocturnal sleep by increasing slow-wave sleep and reducing REM fragmentation; it also reduces daytime slow-wave and REM sleep [73]. Given the rapidity of its pharmacokinetics, it must be taken as a twice-nightly dose [60].

In a study of 136 patients with narcolepsy, sodium oxybate was associated with reduced ESS scores, reduced cataplexy, and improved CGI-C scores [74]. In a similar study of 118 patients, sodium oxybate was associated with reduced cataplexy, daytime sleepiness, inadvertent sleep attacks and night-time awakenings. In a 12-month, open-label extension trial, adverse events were generally mild [75]. Finally, a study of 228 adult patients from the USA, Canada and Europe reported that treatment with sodium oxybate improved MWT results, decreased ESS scores and increased CGI-C scores compared to placebo [76].

Common side-effects are nausea, dizziness, enuresis and anxiety. Given the potential for respiratory depression, it should not be mixed with alcohol or other sedatives [46]; OSA should also be excluded before commencing treatment.

Sodium oxybate is recommended as first-line treatment of EDS occurring with cataplexy and disturbed night sleep. It is the only first-line agent that addresses the major symptoms of narcolepsy as monotherapy. It is also recommended as second-line treatment if monotherapy with another agent has failed [65].

Novel therapies

FT218

FT218 is a controlled-release formulation of sodium oxybate. It comprises a microparticulate platform that facilitates administration as a single rather than twice-nightly dose [77]. The efficacy and safety of FT218 were assessed in the phase III REST-ON trial. 222 patients were randomised to receive placebo or one of four doses of FT218. All four doses were associated with improvements in ESS score while the 9-g dose showed reduced cataplexy and a higher proportion of patients with improved CGI-I (Clinical Global Impression of Improvement) ratings. Common adverse events were nausea, vomiting, headache and dizziness [78]. The FT218 formulation of sodium oxybate is currently under review by the US Food and Drug Administration for the indication of EDS and cataplexy in narcolepsy patients [79]. The RESTORE trial is currently evaluating the long-term safety and tolerability of FT218 and is due to be completed in June 2023 (ClinicalTrials.gov identifier NCT04451668).

Lower-sodium oxybate

Sodium oxybate adds between 1100 and 1640 mg of sodium to daily sodium intake. Given that narcolepsy is associated with obesity, diabetes and increased cardiovascular risk [38, 41, 42], low-sodium preparations of sodium oxybate may reduce cardiovascular risk in these patients. Lower-sodium oxybate is a formulation of sodium oxybate, potassium oxybate, calcium oxybate and magnesium oxybate. Its sodium content is 92% less than sodium oxybate. Its efficacy and safety was assessed in a phase III trial of 211 patients using a double-blind, randomised withdrawal period design. Withdrawal from lower-sodium oxybate was associated with increases in cataplexy attacks and ESS scores. Headache, dizziness and nausea were the most common adverse effects [80].

TAK-925

TAK-925 is a selective orexin 2 receptor agonist that can be administered by a 9-h intravenous infusion for 7 days. Tanaka *et al.* [81] conducted a randomised, double-blind, placebo-controlled, multiple-ascending-dose phase I study in 13 patients with type 1 narcolepsy. During the 7-day infusion, patients who received TAK-925 had reduced cataplexy and reduced ESS scores. The authors argued that these results support further research into orexin agonists as a therapeutic option in narcolepsy patients.

TS-091

TS-091 (enerisant) is a histamine H3 antagonist/inverse agonist that has been evaluated in two phase II, double-blind, placebo-controlled trials. In the first study, the dose of 50 mg (but not 25 mg or 100 mg) was associated with significant reductions in ESS score; however, these doses were poorly tolerated due to high incidence of insomnia, headache and nausea. In the second study, the doses of 5 mg and 10 mg were associated with less adverse events but with no significant effect on MWT or ESS scores. The authors could not determine an optimal dose of TS-091 and suggested that tailored dosing adjustments may be required [82].

Future directions

Future research into narcolepsy should have two main priorities. First, novel methods of restoring orexin to the central nervous system are necessary. Intranasal [83] and intravenous [81] delivery of orexin have been attempted in humans, while intracerebroventricular delivery has been attempted in animal models [24, 84]. However, these experiments have been undermined by a lack of efficacy or difficult logistics.

Secondly, a more precise understanding of the destruction of orexin-secreting neurons is required. Greater insight into the pathogenesis could facilitate discovery of biomarkers that identify patients in the early stages of neuron destruction. In this instance, immunotherapy could be offered to these patients in the hope of arresting orexin depletion and preserving a normal sleep–wake cycle [85].

Other central disorders of hypersomnolence

The next sections of this review will discuss other central disorders of hypersomnolence. Key clinical and diagnostic features of these, as well as of narcolepsy, are summarised in table 2.

Idiopathic hypersomnia

Idiopathic hypersomnia is a disorder characterised by EDS. The typical history is of a young adult, mean age of onset approximately 20 years, complaining of persistent EDS along with deterioration in attention and ability to focus, and memory impairment. Total sleep time may be prolonged in some patients. Naps are typically not restorative, in contrast to type 2 narcolepsy, where short naps may be refreshing [87]. Patients also frequently describe “sleep drunkenness”, a phenomenon synonymous with severe sleep inertia, characterised by extreme difficulty waking, necessity to return to sleep, and transient confusion on waking [88]. Idiopathic hypersomnia patients may report a profound impact on quality of life and ability to function [89]. Depressive symptoms are reported in 15–25% of patients with idiopathic hypersomnia. However, this is a complex association because hypersomnolence may also occur in depressive disorders (which should be classified as hypersomnolence related to a psychiatric condition). In some patients there may be bi-directional effects [90].

The International Classification of Sleep Disorders, third edition (ICSD-3) diagnostic criteria require a history of “daily irrepressible sleep” lasting longer than 3 months without a history of cataplexy. Evidence of hypersomnolence can be either 1) total 24-h sleep time >660 min on 24-h PSG or 7-day actigraphy, or 2) mean sleep latency <8 min and <2 SOREMPs on overnight PSG and MSLT considered together [86].

In the largest meta-analysis to date, Zhang *et al.* [91] found that, although patients with type 2 narcolepsy had increased REM percentage and decreased REM latency compared with idiopathic hypersomnia, there was no significant difference in other PSG parameters (including arousal index, both N1 and N2 sleep stage percentage, sleep efficiency and sleep latency). Multiple overlapping features, along with lack of reliable biomarkers, have led to the suggestion that the disorders (type 2 narcolepsy and idiopathic hypersomnia) represent a heterogenous spectrum of sleep disorders [92].

In contrast to narcolepsy, behaviour modification is rarely an effective treatment. Sleep hygiene modification and timed naps do not reduce sleepiness. First-line therapy is modafinil. Methylphenidate and pitolisant are also utilised as wake-promoting agents [93]. Recently, lower-sodium oxybate has been shown to improve EDS and Idiopathic Hypersomnia Severity Scale scores in patients with idiopathic hypersomnia [94].

TABLE 2 Key clinical and diagnostic features of narcolepsy and other central disorders of hypersomnolence

	Clinical features in addition to EDS to help differentiate	Distinguishing features on diagnostic testing
Type 1 narcolepsy	Cataplexy (sudden loss of muscle tone in response to emotion) is pathognomonic Hypnagogic hallucinations and sleep paralysis in 50–60% of patients Disturbed nocturnal sleep	Actigraphy: >6 h·night^{-1} PSG: SOREMP suggestive of diagnosis Fragmented nocturnal sleep ± Increased EMG tone during REM MSLT: short sleep latency ⩽8 min and ⩾2 SOREMPs CSF orexin levels: low ⩽110 pg·mL^{-1} or <1/3 of mean values in normal subjects; often undetectable
Type 2 narcolepsy	As type 1 narcolepsy but no cataplexy	Actigraphy: >6 h·night^{-1} MSLT: short sleep latency ⩽8 min and ⩾2 SOREMPs CSF orexin levels: normal or intermediate >110 pg·mL^{-1} or >1/3 of mean values in normal subjects
Idiopathic hypersomnia	Sleep drunkenness/sleep inertia on awakening Non-refreshing naps ± Long sleep times	Actigraphy: regular or long sleep times (diagnosis can be made if average 24-h sleep time >660 min over ⩾7 days) PSG: may show high sleep efficiency, increased slow-wave sleep MSLT: short sleep latency ⩽8 min and <2 SOREMPs
Kleine–Levin syndrome	Episodes of recurrent hypersomnia (1–4 weeks) with neuropsychiatric features Asymptomatic between episodes	PSG normal between events EEG may show slowing during episode
Hypersomnia due to a medical disorder	EDS with associated features of a particular condition such as Parkinson disease, stroke, *etc*.	
Hypersomnia associated with a psychiatric disorder	EDS in patients with a psychiatric condition Atypical depression may have a similar phenotype to idiopathic hypersomnia	MSLT: sleep latency may be normal or short, rarely SOREMP
Hypersomnia due to a medication or substance	EDS related to medication: careful review of medication history and consideration of urine toxicology	MSLT may show short sleep latency, confounding diagnosis if medication effect not suspected Urine toxicology as part of MSLT protocol is helpful
Insufficient sleep syndrome	Chronic EDS due to sleep deprivation	Actigraphy: irregular/insufficent sleep times PSG: reduced sleep latency, high sleep efficiency, increased slow-wave sleep MSLT: sleep latency short, occasionally SOREMP

Data from the International Classification of Sleep Disorders, third edition [86]. EDS: excessive daytime sleepiness; PSG: polysomnography; SOREMP: sleep-onset rapid eye movement period; EMG: electromyogram; REM: rapid eye movement; MSLT: multiple sleep latency test; CSF: cerebrospinal fluid; EEG: electroencephalogram.

Kleine–Levin syndrome

Kleine–Levin syndrome (KLS), or recurrent hypersomnia, typically presents in adolescence to young adulthood and is characterised by recurrent episodes of hypersomnolence with accompanying cognitive and behavioural disturbance.

In 1925, the German neuropsychiatrist Willi Kleine published “Periodic somnolence”, which described a series of patients with episodes of profound sleepiness accompanied by mood disturbance, apathy and alteration in eating habits [95]. Neuropsychiatrist Max Levin subsequently published “Periodic somnolence and morbid hunger: a new syndrome” [96]. The lasting moniker was coined by British neurologist MacDonald Critchley, who in 1942 published a report of “episodic somnolence and morbid hunger” in two servicemen of the Royal Navy [97].

KLS is considered a markedly rare disease. Where examined, prevalence estimates range from 1.8 per million people in France [98] to 3.19 per million people in Switzerland [99]. It is not exclusive to a particular region, with documented cases throughout Europe, Asia, Africa and the Americas [100, 101].

The underlying aetiology of KLS is not known. Higher prevalence of HLA DQB1*0201 was found in one cohort compared to matched controls [102]; however, this has not been replicated in larger series [98, 100, 101]. A positive relationship between episode occurrence and viral upper respiratory tract infection was identified

in Taiwan [103]. KLS is associated with a number of conditions, including genetic or developmental diseases such as Asperger syndrome, intellectual disability, stroke and encephalitis [98, 100, 101].

The illness presents more commonly in males, with a median age of onset of 16 years. Episodes last on average 10 days. A small percentage of patients will have a decrease in frequency, severity or duration of episodes over time [101]. In addition to EDS, behavioural symptoms include profound apathy and abulia, compulsive eating, hypersexuality, low mood and a distortion of reality. As the key feature in a disorder of hypersomnolence, patients with KLS sleep more, up to 18 h per day, and can lose circadian rhythm. They are often difficult to wake, with reports of profound hypnagogic hallucinations without sleep paralysis. Patients are often found asleep.

Widely accepted diagnostic criteria for KLS are defined in the ICSD-3. First, the patient must have two recurrent episodes of EDS, lasting between 2 days and 5 weeks and occurring at least once every 18 months. Importantly, complete recovery must be observed between episodes, with return of a normal sleep–wake cycle and baseline cognitive function, behaviour and mood. During the episode, patients must also exhibit at least one of the following: cognitive dysfunction, altered perception, an eating disorder (either anorexia or hyperphagia) and disinhibited behaviour (often presenting as hypersexuality). Finally, the symptoms cannot be explained by another cause [86]. In contrast to idiopathic hypersomnia, where the key to diagnosis lies in features that distinguish it from narcolepsy, the differential diagnosis of KLS includes a psychiatric cause, particularly bipolar disorder, other neurological disease, such as migraine, epilepsy or hypothalamic lesion, or medication effect.

In stark contrast to other disorders of hypersomnolence, KLS patients are typically well between episodes; therefore, long-term medication use is often not indicated. Treatment options, which include overlap with other disorders of hypersomnolence, include conservative management techniques including reassurance, and techniques for management and improving sleep hygiene [104]. Pharmacological options have not been validated in RCTs. During acute episodes, symptomatic treatments may be used, such as methylphenidate and modafinil, amantadine and antipsychotic medication such as risperidone, whereas for prevention of recurrence, lithium has been the most commonly used, but care must be taken in assessing risk–benefit and monitoring for side-effects (including renal or thyroid dysfunction). Alternatively, a mood-stabilising anti-epileptic medication such as valproic acid or carbamazepine could be considered [104, 105].

Hypersomnolence related to a medical or psychiatric condition or medication effect

EDS may be associated with Parkinson disease [106, 107], structural brain lesions [108, 109], encephalitis [110], diabetes [111] and obesity [112]. Hypersomnia is common following traumatic brain injury and, in over a quarter of patients, sleepiness may persist at 1 year following the injury [113]. Hypersomnia also frequently occurs in psychiatric disorders [114]. Atypical depression, in particular, can present with a similar phenotype to idiopathic hypersomnia.

Many prescribed medications can cause EDS, including hypnotics causing next-day sedation, anti-epileptic medications, and dopamine agonists which can cause “sleep attacks” [115–117]. In one study, one-third of patients assessed for subjective hypersomnia had a positive urine toxicology for a substance affecting sleep, such as opioids or cannabis [118].

Insufficient sleep syndrome

Behaviourally insufficient sleep is a common mimic of narcolepsy and idiopathic hypersomnia. The prevalence is unknown. However, in a large registry of patients being assessed at a tertiary sleep clinic, 5.5% of patients were diagnosed with insufficient sleep syndrome [119]. Other studies have estimated prevalence rates of 10% in high-school and college students [120, 121].

Patients may have EDS and longer sleep duration during weekends or vacations. PSG may show short sleep latency, high sleep efficiency, and increased slow-wave sleep. MSLT may show short mean sleep latency and even SOREMPs, mimicking narcolepsy. Actigraphy prior to the study can reveal a pattern of sleep deprivation.

Confirmation of definite insufficient sleep syndrome by ICSD-3 criteria requires resolution of sleepiness with extension of sleep time, but this is challenging to complete even under optimal conditions. In a research study, only 39% of 94 patients successfully achieved actigraphically documented sleep extension with resolution of symptoms, despite multiple attempts, probably due to competing priorities such as work and family responsibilities. This reflects the challenges in treating this condition in modern society, as it is

difficult for patients to make the necessary adjustments even with diagnosis and education. However, insufficient sleep syndrome is linked to metabolic and neurodegenerative diseases, lower academic performance and higher risk of accidents, so it represents a significant public health issue [122].

Conclusion

Narcolepsy is a rare disease with significant impact on daytime function and quality of life. Early and accurate diagnosis allows intervention with effective treatment, which at this time is symptomatic, but in the future more targeted treatments, such as orexin agonists or immunotherapy, may be available. Other central disorders of hypersomnolence can be distinguished with careful clinical history and comprehensive sleep studies.

Important information to disseminate to all patients with EDS related to central disorders of hypersomnolence includes documented advice on driving guidelines in accordance with local regulations, avoiding potentially dangerous professional or recreational activity, and keeping a sleep diary.

Key points

- Type 1 narcolepsy is characterised by the pentad of EDS, cataplexy (sudden loss of muscle tone triggered by emotion, typically laughter), sleep paralysis, hypnagogic hallucinations and disrupted nocturnal sleep.
- There is often a significant delay in diagnosis (up to 15 years), so awareness of the condition is vital.
- Insufficient sleep syndrome is a common cause of EDS and often mimics narcolepsy and idiopathic hypersomnia.

Self-evaluation questions

1. Cataplexy is a cardinal feature of which condition?
    a) Type 1 narcolepsy
    b) Type 2 narcolepsy
    c) Idiopathic hypersomnia
    d) Kleine–Levin syndrome
2. Type 1 narcolepsy is characterised by deficiency of which neurotransmitter?
    a) Serotonin
    b) Dopamine
    c) Orexin
    d) Histamine
3. Which of the following would describe the proposed pathophysiology of type 1 narcolepsy?
    a) Metabolic
    b) T-cell-mediated
    c) Neurodegenerative
    d) Hereditary
4. Patients with idiopathic hypersomnia experience which of the following? Choose all that apply.
    a) Excessive daytime sleepiness
    b) Sleep drunkenness/sleep inertia
    c) Hypersexuality
    d) Compulsive eating

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Suggested answers

1. a
2. c
3. b
4. a, b