Narcolepsy — clinical spectrum, aetiopathophysiology, diagnosis and treatment

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Abstract | Narcolepsy is a rare brain disorder that reflects a selective loss or dysfunction of orexin (also known as hypocretin) neurons of the lateral hypothalamus. Narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness and cataplexy, accompanied by sleep–wake symptoms, such as hallucinations, sleep paralysis and disturbed sleep. Diagnosis is based on these clinical features and supported by biomarkers: evidence of rapid eye movement sleep periods soon after sleep onset; cerebrospinal fluid orexin deficiency; and positivity for HLA-DQB1*06:02. Symptomatic treatment with stimulant and anticataplectic drugs is usually efficacious. This Review focuses on our current understanding of how genetic, environmental and immune-related factors contribute to a prominent (but not isolated) orexin signalling deficiency in patients with NT1. Data supporting the view of NT1 as a hypothalamic disorder affecting not only sleep–wake but also motor, psychiatric, emotional, cognitive, metabolic and autonomic functions are presented, along with uncertainties concerning the 'narcoleptic borderland', including narcolepsy type 2 (NT2). The limitations of current diagnostic criteria for narcolepsy are discussed, and a possible new classification system incorporating the borderland conditions is presented. Finally, advances and obstacles in the symptomatic and causal treatment of narcolepsy are reviewed.

Although narcolepsy had previously been described in the literature[1], three publications by Westphal, Gélinau and Fischer in the late 19th century (1877–1880)[2–4] were the first to clearly identify the two main manifestations of narcolepsy: an irresistible or imperative excessive daytime sleepiness (EDS) and brief episodes of loss of muscle tone or control triggered by emotions and accompanied by a preserved state of consciousness (variously termed astasia, catalepsy and cataplexy)[5]. Later researchers confirmed these observations[6,7], but narcolepsy was generally considered to be a rare (by 1924, only 35 patients had been reported) and nonspecific manifestation of other diseases[8]. By 1960, however, the main clinical features of narcolepsy had been precisely described in large case series that definitively established the specificity of the disease[8–11].

Classic or typical narcolepsy, now termed narcolepsy type 1 (NT1), is characterized by the presence of cataplexy and orexin deficiency. By contrast, narcolepsy without either cataplexy or orexin deficiency — now termed narcolepsy type 2 (NT2) — remains poorly understood. Although the existence of mild and incomplete presentations of narcolepsy (the 'narcoleptic borderland') is generally accepted, their inclusion within the diagnosis was (and still remains) controversial[12,13].

In the past 20 years, considerable advances have been made in our understanding of the clinical manifestations, aetiology, pathophysiology, diagnosis and management of narcolepsy. Several biomarkers of narcolepsy have also been established, including polysomnography findings of sleep-onset rapid eye movement (REM) sleep periods (SOREMPs)[14], positivity for HLA-DQB1*06:02 (REFS[15,16]) and orexin deficiency in cerebrospinal fluid (CSF)[17]. These biomarkers have improved diagnostic certainty and opened new avenues of research[18]. The purpose of this Review is to provide an update on these advances, discuss the unsolved challenges and present perspectives for the future.

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Key points

- Narcolepsy is a rare and often disabling hypothalamic disorder that presents with sleep–wake dysregulation (excessive daytime sleepiness (EDS), cataplexy, hallucinations, sleep paralysis and disturbed sleep) and motor, cognitive, psychiatric, metabolic and autonomic disturbances.
- Narcolepsy arises from the interaction of genetic and environmental factors, which lead to an immune-mediated selective loss or dysfunction of orexin neurons in the lateral hypothalamus.
- Patients with narcolepsy type 1 have cataplexy and little or no orexin in cerebrospinal fluid; narcolepsy type 2 is a diagnosis of exclusion requiring ancillary tests ruling out other causes of EDS.
- Several drugs (including modafinil, sodium oxybate, pitolisant, solriamfetol and methylphenidate) improve narcoleptic symptoms in most patients.
- More research is needed to understand the clinical spectrum of narcolepsy, the exact mechanisms leading to orexin neuronal loss and the value of new treatments, including orexin agonists and immunomodulation.
- Awareness of narcolepsy, assessments of treatment efficacy, treatment of children or during pregnancy and management of comorbidities are still suboptimal in narcolepsy and require improvement.

by the European Sleep Foundation with the support of the Grawe Foundation and held during 2–4 July 2015 in Ticino, Switzerland. The Think Tank comprised 6 workshops on various aspects of narcolepsy (plus opening and closing sessions) attended by 19 invited experts from all over the world.

Epidemiology

The prevalence of narcolepsy in Europe and North America is estimated to be ~200–500 per million individuals[19–22]. Because of uncertainties concerning the narcoleptic borderland (particularly NT2, discussed below), the exact incidence of narcolepsy remains unknown. The highest prevalence of narcolepsy occurs in Japanese populations (1,600 per million individuals), although this estimate comes from studies with uncertain methodology. The lowest prevalence occurs in Jewish and Arabic populations (2–40 per million individuals)[19,23,24]. In some series, narcolepsy affected more male than female individuals[24]. Genetic and environmental factors probably contribute to these differences. Data indicating increased mortality in patients with narcolepsy remain controversial[25,26].

Narcolepsy usually starts in adolescence, and a small second peak of onset occurs at around age 35 years[27]. In 10–15% of patients, narcolepsy starts before the age of 10 years[28]. However, narcolepsy in children was only rarely systematically studied before the current century[29–31].

Narcolepsy can have an acute course, in which symptoms develop within a few days or weeks after a triggering event, such as vaccination, stress or head trauma, a chronic course, in which the onset of symptoms is difficult to determine, or a progressive course, in which the onset of different symptoms is separated by years or even decades[32]. These differing presentations probably reflect different pathophysiological mechanisms[32]. In a series of 1,099 patients with narcolepsy, cataplexy most often developed at the same time as EDS in 49% of the cohort and developed after EDS in another 43%[33]. Cataplexy preceded EDS in only 8% of the patients. The interval between onset of EDS and onset of cataplexy is usually <2–3 years but can exceed 40–50 years[33–36]. Narcolepsy without cataplexy can be transient, and patients can

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enter remission[37,38], whereas narcolepsy with cataplexy typically does not remit (remission of this presentation has been reported only once, in a patient who received immunotherapy soon after disease onset[39]). In addition, narcoleptic symptoms often improve over time; the severity of EDS and cataplexy typically decreases with age, possibly as a result of coping mechanisms.

Aetiology

By the 1920s, the possibility of an infectious and post-traumatic origin of narcolepsy had already been proposed[8,40,41]. In the early 1980s, evidence that narcolepsy was associated with the HLA system suggested involvement of the immune system in its pathogenesis[15,16,42]. The demonstration of low CSF levels of orexin A (and shortly thereafter of the selective loss of orexin neurons in the lateral hypothalamus) in patients with narcolepsy raised the possibility that these cells were the target of such a process[17,43–45].

Orexin A and orexin B are small neuropeptides that excite target neurons through orexin receptors type 1 and type 2, respectively[46,47]. Loss of this crucial system disrupts the functioning of multiple frontal, limbic, diencephalic and brainstem networks and results in the symptoms of narcolepsy[48–50]. This dysfunction has been conceptualized as a state of instability or loss of boundary control that manifests as an inability to remain in sleep or wake states for the normal length of time and by the inappropriate occurrence of sleep phenomena during wakefulness, and vice versa[51]. Therefore, bouts of both wakefulness and sleep are short in patients with narcolepsy, REM sleep atonia occurs during wakefulness (cataplexy), and dreaming can occur at sleep–wake and wake–sleep transitions (hypnagogic or hypnopompic hallucinations). However, the existence of patients with narcolepsy with and without cataplexy who have normal CSF levels of orexin, and of patients with low or absent orexin levels in CSF secondary to hypothalamic damage who do not have narcolepsy or cataplexy symptoms, raises the possibility that a deficiency in orexin production is not (always) necessary nor (always) sufficient to cause narcolepsy in humans[52–57].

Today, narcolepsy is considered to arise from multiple hits: the co-occurrence of genetic predisposition, environmental factors and triggering events eventually leads to the selective, immune-mediated destruction, dysfunction or silencing of orexin-producing neurons. One study, published by some of the authors of this Review in 2018, reported the presence of autoreactive $CD8^+$ and $CD4^+$ T cells in NT1 and NT2 (REF.[58]). Three subsequent reports, published in the past few months, provide further support to the hypothesis of a pivotal role of specific T cells in the neuronal damage seen in human narcolepsy[59–61]. The following discussion is devoted, unless otherwise specified, to NT1.

Pathological findings

Three autopsy series of patients with NT1 revealed a selective loss of ~90% (range 75–95%) of the 50,000–70,000 orexin neurons in the lateral hypothalamus[43,62,63]. It is possible that some neurons are undetectable (owing to silencing of orexin expression) but not irreversibly lost. No other adjacent neurons of the lateral hypothalamus were affected (such as those producing melanin-concentrating hormone (MCH)). The brain tissues showed increased gliosis but no inflammatory or neurodegenerative changes[62,64].

In animal models, partial loss of orexin neurons leads to narcolepsy without cataplexy and with normal CSF orexin levels[62,65]. In two patients with NT2, one had a normal number of orexin neurons and one had a 33% decrease in orexin neurons[62]. Of note, this decrease occurred mainly in the posterior hypothalamus. Interestingly, two independent teams have reported an increased number of histamine neurons (>50% higher than in healthy individuals) in the tuberomammillary nucleus in patients with NT1 and in mouse models of narcolepsy[63,66]. This observation possibly reflects a compensatory response to the loss of orexinergic excitatory drive. However, this interpretation is controversial and limitations in the methods used to detect histamine neurons represent an alternative explanation[63,66].

Genetic and epigenetic factors

In twin studies[67–70], only ~25% of monozygotic twin pairs are concordant for narcolepsy[29]. Familial narcolepsy represents 1–2% of cases. Less than 2% of individuals with narcolepsy have more than 1 affected family member, and multiplex families (those with more than 2 members who have cataplexy) are rare[69–72].

Narcolepsy is closely associated with the HLA class II region, which encodes molecules that present antigenic peptides to $CD4^+$ T cells[15]. Systematic studies demonstrated that HLA-DQB1*06:02 is expressed in 86–98% of patients who have NT1 and in ~40–50% of patients with NT2 (REFS[73,74]). However, HLA-DQB1*06:02 is also expressed in 5–38% of the general population[73,74], and only 1 in 1,000 carriers of this allele will develop narcolepsy[71,74]. In addition, HLA-DQB1*06:02 positivity in the general population is associated with shorter REM sleep latencies, suggesting the possibility that this sleep EEG finding might represent a (first) biomarker of an increased risk of developing narcolepsy[75]. The low frequency of this allele in Jewish and Saudi populations might explain the rarity of narcolepsy in these groups[23,24]. Other HLA class II alleles are also associated with narcolepsy, albeit to a lesser extent[73,74,76,77].

Weak associations with narcolepsy have also been reported for HLA class I genes (A, B and C), which encode molecules that present antigenic peptides to $CD8^+$ T cells. This observation suggests that patients with narcolepsy might have an increased genetic susceptibility to infections and that this disease involves cytotoxic immune mechanisms[76,78]. These studies also identified protective alleles in both HLA class I and class II genes, which might play a part in the delay (or even absence) of evolution of NT2 to NT1 seen in some patients[74,76,79]. Genome-wide association studies found that polymorphisms in *TRAC* (encoding the T cell receptor α-constant domain) were also associated with susceptibility to narcolepsy, which further supports the hypothesis that narcolepsy is an immune-mediated disease[77,80].

Other studies have identified associations between narcolepsy and polymorphisms in other immune-related

genes, including *P2RY11* (encoding P2Y purinoceptor 11, a modulator of the autoimmune response to infection), *CTSH* (encoding pro-cathepsin H) and *TNFSF4* (encoding tumour necrosis factor (TNF) ligand superfamily member 4)[74,81–83]. Gene sequencing studies in patients with rare familial narcolepsy with cataplexy have not shown any consistent associations, although mutations have been found in *HCRT* (encoding orexin), *MOG* (encoding myelin oligodendrocyte glycoprotein) and *P2RY11* genes, which modulate the immune response[43,69,70].

An epigenome-wide association study published in 2018 found that the genes containing the top-ranked differentially methylated DNA sites in patients with narcolepsy were associated with pathways of hormone secretion and monocarboxylic acid metabolism. The top-ranked narcolepsy-associated differentially methylated DNA sites were particularly abundant in non-CpG island regions, and >95% of these sites were hypomethylated in patients with narcolepsy[84].

Environmental factors

The low concordance for narcolepsy with cataplexy in monozygotic twins points to a contribution of environmental factors[67,68,85–87]. Season of birth was associated with the risk of narcolepsy in some but not all studies, which suggested that exposure to viruses, bacteria or toxins early in life might alter the development of the immune system and thereby predispose individuals to narcolepsy[88–91]. Subsequent exposure to these or other environmental factors (such as infections) might reactivate or trigger an immune response that leads to the destruction of orexin neurons.

A temporal association between influenza or encephalitis epidemic infections and the onset of narcolepsy was first noted in the 1920s[8,40,41,92]. In 2009, the finding of elevated titres of anti-streptococcal antibodies in patients with recent-onset narcolepsy suggested an association with other upper airway infections, particularly β-haemolytic streptococcal infections[93]. The most important association with infection involves the influenza A virus subtype H1N1. Following the 2009–2010 vaccination campaign against pandemic H1N1 influenza, a statistically significant sixfold to ninefold increase in the risk of narcolepsy was reported in Finland and other northern European countries where the Pandemrix vaccine had been used[94,95]. Differences in vaccine content might explain why this association was not observed with any other influenza vaccines[96,97]. In the absence of vaccination, a peak in the incidence of H1N1 infection was seen in China in late 2009, which was followed during the winter of 2009–2010 by a threefold increase in the incidence of narcolepsy compared with both previous and subsequent years[98]. However, this peak in narcolepsy incidence was not observed in Taiwan despite its exposure to the same epidemic[99]. A trend towards earlier onset of narcolepsy in childhood might also be related to the influenza H1N1 pandemic of 2010–2011. These observations suggest that influenza H1N1 infection itself, as well as some influenza vaccines, might trigger the development of narcolepsy. An immunological study published in 2019 suggests the possibility that an autoimmune process targeting orexin neurons might be triggered by molecular mimicry of a particular piece of the influenza haemagglutinin protein[60]. Narcolepsy has also been reported to occur following other vaccinations, although these relationships could be coincidental or not causal[100,101]. Finally, narcolepsy has occasionally been reported to occur after traumatic brain injury[8,102,103].

Immunological mechanisms

A few types of autoantibodies have been identified in sera from patients with narcolepsy[104,105]. These antibodies were, however, also detected in sera from patients with other sleep disorders and sera from healthy controls. In addition, passive transfer experiments involving these autoantibodies did not reproduce narcolepsy in animal models. However, indirect evidence of an autoimmune pathogenesis of narcolepsy is provided by the observation that narcolepsy occasionally occurs in association with paraneoplastic syndromes and other autoimmune diseases, such as multiple sclerosis, coeliac disease and systemic lupus erythematosus[5,106–111]. In addition, a few patients with narcolepsy respond to immunomodulatory treatment[39,112–114].

The environmental and genetic factors discussed in the preceding sections represent circumstantial evidence that an autoimmune process contributes to narcolepsy. Additional ancillary findings in humans offer further support for this hypothesis. Although evidence of disease-specific antibodies is lacking, inflammatory findings in CSF (namely, pleocytosis and oligoclonal bands) can occasionally be observed[115–119]. Increased levels of specific cytokines (TNF and IFNγ) and $CD4^+$ T cells, and activation of $CD4^+$ and $CD8^+$ T cells, have also been reported in sera (and to some extent also in CSF)[120–123]. In 2018, some authors of this Review reported having identified autoreactive $CD4^+$ and $CD8^+$ T cells in patients with NT1 and NT2 that specifically target antigens expressed by orexin neurons[58]. In accordance with this observation, two subsequent papers similarly reported the presence of autoreactive $CD8^+$ and $CD4^+$ T cells in patients with NT1 (REFS[59–61]).

Clinical features

Narcolepsy presents with a variable combination of sleep–wake symptoms and motor, psychiatric, emotional, cognitive, metabolic and autonomic disturbances that reflect the hypothalamic origin of the disorder (BOX 1). The following discussion of the clinical symptoms of narcolepsy refers to NT1 unless otherwise specified.

Excessive daytime sleepiness

EDS is usually the leading (and most disabling) symptom in most patients with narcolepsy and typically presents as an inability to stay awake but is also reported as a subjective feeling of sleepiness accompanied by difficulties in sustaining attention (FIG. 1). EDS is often already present in the morning hours and is typically irresistible, with rapid transitions into sleep (so-called sleep attacks). Involuntary napping was reported by 80% of 1,079 patients in a large European study[124]. These episodes predominantly occur in monotonous situations but can also occur when patients are active. Naps are typically but not invariably short (15–20 min),

Box 1 | **Narcolepsy symptoms and associated features**

The relative frequencies of these features are presented in the text.

Leading symptoms

- Excessive daytime sleepiness (which can also manifest with sleep attacks, involuntary napping, automatic behaviours, difficulty sustaining attention and memory disturbances)
- Cataplexy (often partial, rarely complete with falls)

Associated sleep–wake symptoms

- Fatigue
- Sleep paralysis
- Hallucinations (visual, auditory and tactile)
- Frequent dreams, nightmares, lucid dreams and enacted dreams
- Disrupted night-time sleep
- Restless legs syndrome
- Parasomnias (including sleepwalking, REM sleep behaviour disorder and nocturnal eating disorder)

Other associated manifestations

- Overweight
- Autonomic disturbances
- Depression, anxiety and functional disorders (such as pseudocataplexy)
- Attention-deficit hyperactivity disorder
- Headache, olfactory dysfunction and digestive disturbances
- Decreased quality of life, car accidents and injuries

Ancillary findings

- Short sleep latencies and disturbed vigilance
- Sleep-onset rapid eye movement (REM) episodes
- Decreased or undetectable levels of orexin A in cerebrospinal fluid
- HLA-DQB1*06:02 positivity
- Polysomnographic findings of sleep-disordered breathing, REM sleep behaviour disorder, periodic limb movements, frequent arousals, stage shifts and loss of REM sleep atonia

refreshing and associated with oneiric experiences[34,125]. Patients can develop so-called automatic behaviours — abnormal waking activities such as putting salt in coffee, writing over the border of a piece of paper or driving to the wrong destination[11,126] — for which they can be amnesiac, meaning that they are experienced as blackouts. Resisting sleep might predispose individuals with narcolepsy to such behaviours, but they can also manifest with nonspecific symptoms such as headache, visual or sensory disturbances and hypoacusis.

Fatigue must be distinguished from EDS. Up to 60% of patients with narcolepsy report fatigue, which is more resistant to therapy than EDS[127,128]. In addition, fatigue can increase the burden of EDS because it impairs daytime activity, which is a major measure to combat EDS.

Cataplexy

Cataplexy is the only specific symptom of narcolepsy. This term refers to brief episodes of bilateral loss of muscle tone triggered by sudden emotions in the presence of a normal state of consciousness[34,129]. Partial attacks are very short (2–10 s) unless the trigger remains present. Loss of muscle tone manifests as face drooping, eyelid closure, sagging of the jaw, dysarthria, passive tongue protrusion and bilateral loss of motor control of the extremities. Atonia of the facial muscles (termed facies cataplectica) with mouth opening and tongue protrusion can also be observed, particularly in children[7,130,131]. Deep tendon reflexes are typically transiently abolished but can persist in partial or mild episodes[13,132]. Babinski sign (dorsiflexion of the big toe in response to stimulation of the sole of the foot, rather than the plantar flexion normally seen in adults) can transiently appear, and Parkinson disease-related tremor might persist[8,133]. A few patients experience complete inability to move (termed cataplectic immobility[5]). Falls are reported by one-third of patients, but injuries are rare[129].

Partial attacks can evolve over seconds to complete attacks, which have a duration ≤2 min; a duration >5 min is unusual and often related to withdrawal of anti-cataplectic medications[129,134]. Unilateral dominance is atypical[135], and attacks involving single muscles are exceptional[10,13]. Hyperkinesias, in the form of phasic (twitching of facial muscles), tonic (tongue protrusion, grimacing or neck extension) and repetitive motor activities, can be superimposed on muscle atonia and lead to the misdiagnosis of epilepsy or a movement disorder[8,130]. These positive motor phenomena might be more common in children and at disease onset[8,34,136–140]. The frequency of attacks varies from dozens per day to a few per year[141].

Mirth with laughter is the most typical trigger; ≤50% of patients experience cataplexy while being tickled[34,129]. Sudden or unexpected triumphant emotions (and, less commonly, aggressive emotions) favour cataplexy and explain its appearance during sports, hunting, playing games (FIG. 2) and sexual intercourse (when it is termed orgasmolepsia)[129,142]. Negative emotions such as anger, fear, embarrassment, pain and sorrow rarely trigger cataplexy[34,129,143]. Consciousness, ocular motility and breathing are usually preserved during cataplexy attacks, although some patients report blurring of vision and a feeling of suffocation. Autonomic symptoms such as blood pressure and pulse changes, sweating, penile erection and involuntary urination are possible[8,144]. Episodes of cataplexy can be associated with EDS, hallucinations, sleep paralysis, dreaming and REM sleep behaviour, particularly when the duration of the attack is long[141].

Sleep paralysis and hallucinations

These symptoms are reported, often in combination, by 50–60% of patients with narcolepsy[33,34]. They can occur at sleep onset (hypnagogic), during the night, on awakening (hypnopompic) and in association with daytime naps. Sleep paralysis describes the inability to speak or move any voluntary muscle and usually occurs during transitions between sleeping and waking. Attacks of sleep paralysis can be accompanied by respiratory distress and (predominantly visual) hallucinations, although in up to 85% of hallucinations, senses other than sight (gustatory, olfactory or vestibular–motor hallucinations) are also involved[145]. The hallucinations can be superimposed on the patient's actual environment (that is, the room where they are).

The feeling of the presence of another person and assault scenarios are occasionally reported. Hallucinations can be frightening and cause fear of sleep. Typically, patients realize immediately afterwards that the experiences are not, or cannot be, real, but the

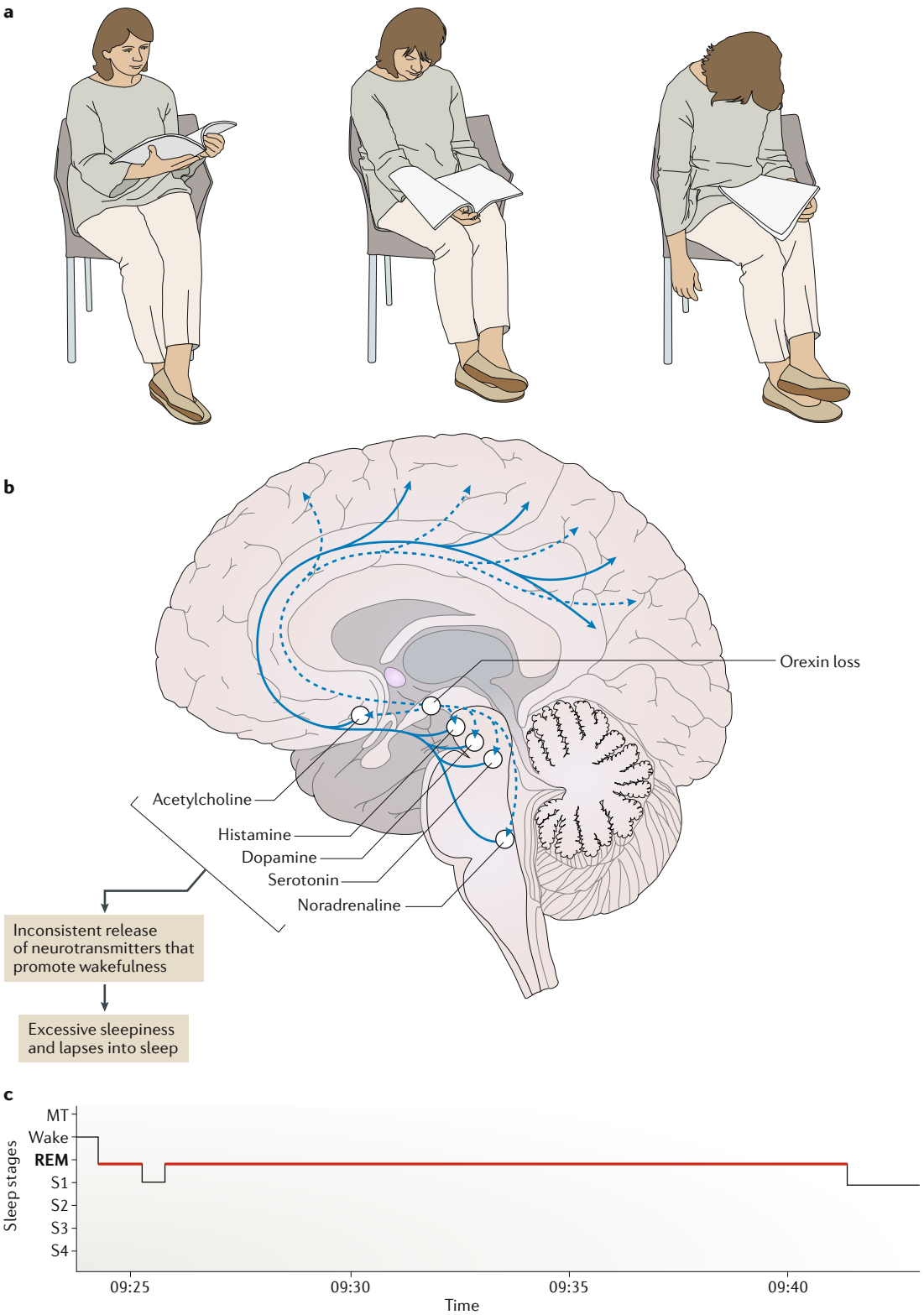


Fig. 1 | **Excessive daytime sleepiness in a patient with narcolepsy. a** | A sleep episode or involuntary nap during quiet reading. Naps can occur in the morning hours and are typically short and refreshing. Sleep episodes are less sudden than cataplexy attacks and are not accompanied by muscle twitches. **b** | The specific loss of orexin-producing neurons in patients with narcolepsy accompanied by cataplexy leads to inconsistent firing of the brainstem neurons responsible for arousal. This change results in excessive daytime sleepiness and a predisposition to lapses into sleep. **c** | A neurophysiological recording made during a multiple sleep latency test (MSLT) documents the transition from wakefulness into sleep. A shortened sleep latency period is evident, and a so-called sleep-onset rapid eye movement (REM) period (SOREMP) occurs within 15 min. In patients with narcolepsy accompanied by cataplexy, SOREMPs occur in ~50% of sleep episodes (detected by MSLT or night-time polysomnography).

hallucinations associated with narcolepsy can be severe enough to prompt a misdiagnosis of schizophrenia[85–87]. Occasionally people with narcolepsy act according to previously experienced dreams without their necessarily being typical hypnagogic hallucinations; these experiences are called dream delusions[146].

Sleep disturbances and parasomnias

Although they often doze, patients with narcolepsy usually do not spend a greater proportion of their time asleep than do people in the general population because narcolepsy is often associated with sleep fragmentation (recurring wake periods during sleep)[147]. Moreover, sleep-onset insomnia is rare in patients with narcolepsy[147]. Occasionally, however, patients with narcolepsy (particularly at disease onset and in childhood) present with long and undisturbed sleep times, sleep inertia or sleep drunkeness[148,149]. The degree of nocturnal sleep disruption is only weakly correlated with EDS[150,151].

Motor control dysfunction in sleep, which might be present from childhood, can present as periodic limb movements (in 25–50% of patients), REM sleep behaviour disorder (RBD) in 25–70% of patients, sleepwalking and nocturnal eating[8,28,152,153]. Periodic limb movements can occur in non-REM and REM sleep as well as in wakefulness and correlate with the severity of EDS and orexin deficiency[154–156]. Restless legs (or limbs) syndrome might also be more frequent in patients with narcolepsy[157]. RBD in these individuals is characterized by elementary rather than complex movements, and its severity correlates with that of cataplexy and orexin deficiency[155,158,159]. Sleep-disordered breathing is also frequent and can be severe, which can delay diagnosis[154,160,161]. Dreams are often reported as vivid and can have archaic or bizarre content and delusional elements[146]. Nightmares and lucid dreaming are more common in patients with narcolepsy than in the general population[162,163].

Psychiatric and emotional disturbances

Until the 1950s, a psychiatric origin for narcolepsy was favoured, in the context of psychoanalytic theories of dreams[164–167]. Indeed, several observations link narcolepsy with psychiatric disease. First, stressful life events can trigger the onset of narcolepsy[168]. Second, psychiatric disturbances are more frequent than in the general population; for example, 20–30% of patients with narcolepsy have depression and anxiety[169–175]. Third, narcolepsy-like symptoms have been reported in patients with schizophrenia and other psychiatric diseases[48,176,177]. Functional disorders associated with pseudocataplectic attacks can also be observed in patients with cataplexy, which complicates treatment choices for these individuals[178,179]. In addition, observations in humans and animal models support the hypothesis that narcolepsy involves a primary dysfunction of reward and emotional processing networks[180–182].

The high frequency of psychiatric disturbances (particularly in children) might reflect the psychosocial burden of narcolepsy, which is comparable to that of epilepsy[28,183]. Narcolepsy is associated with decreased quality of life and an increased risk of car accidents, injuries and other health problems[25,172,184–186]. Patients also have an increased incidence of psychiatric comorbidities, poor school performance, occupational problems, reduced self-esteem and interpersonal problems[170,173,187–189].

Cognitive disturbances

Attention-deficit hyperactivity disorder (ADHD), decreased cognitive performance, altered executive functioning, difficulty in sustaining attention and difficulties with decision making are all found in patients with narcolepsy[190,191]. These cognitive changes are considered to be mainly a consequence of EDS[192–194]. However, an adverse effect of orexin loss on the turnover of (toxic) intracerebral proteins and neurodegenerative changes has also been postulated[195,196].

Metabolic disturbances

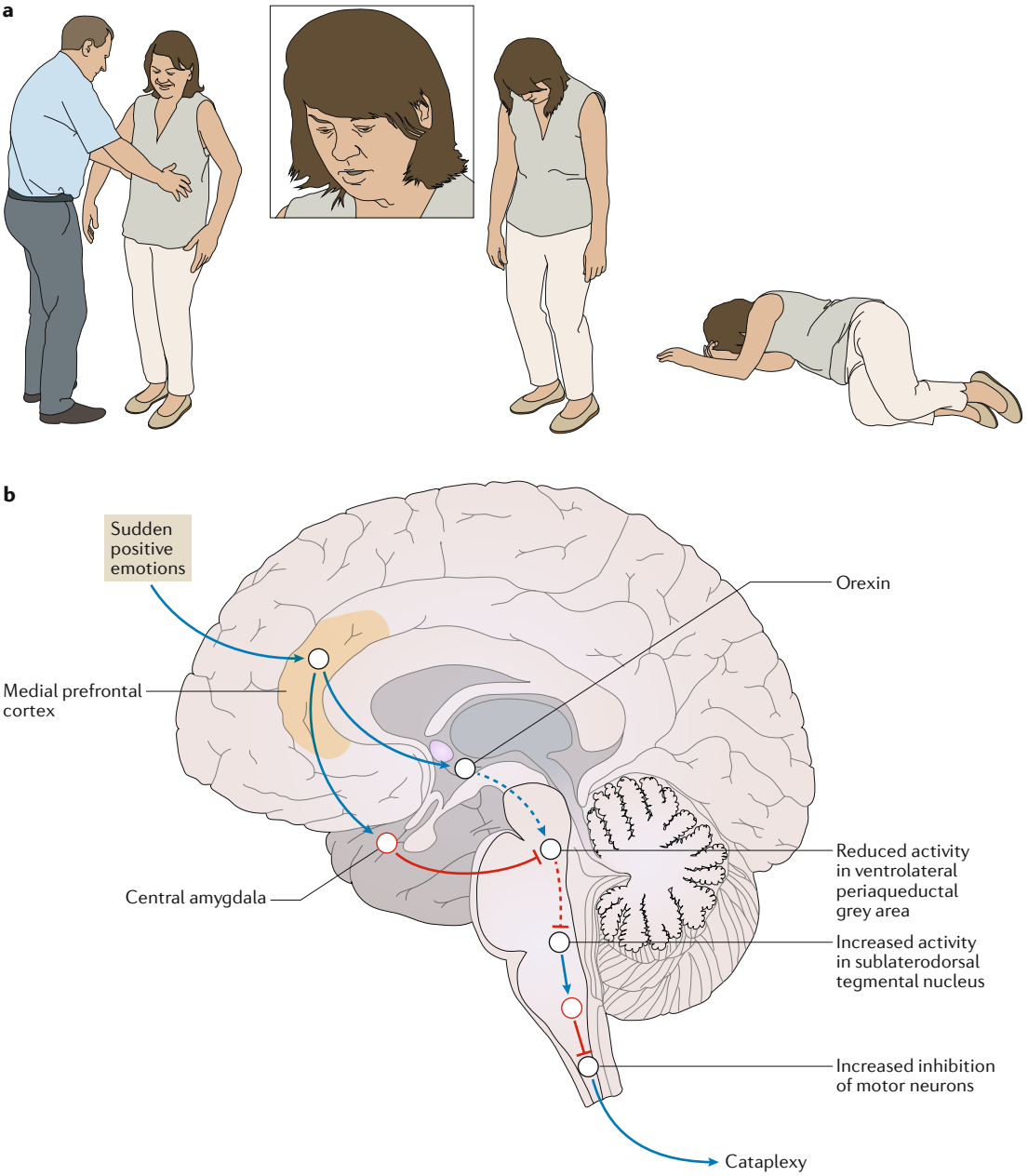
In the early 1920s, overweight was first recognized to be common in patients with narcolepsy and cataplexy[8,9]. BMI is 10–20% higher in individuals with narcolepsy than in the general population[28,197–199]. Patients with narcolepsy have a reduced rate of lipolysis and remain insulin-sensitive despite an increased prevalence of diabetes mellitus, which is probably explained by their increased BMI[200]. Reduced metabolic rate, decreased motor activity and abnormal eating behaviours were observed in some studies[28,199,201–204]. These changes are thought to arise from an underlying hypothalamo-pituitary dysfunction, which could also explain the increased frequency of precocious puberty[28,199,201–204] among individuals with narcolepsy.

Autonomic disturbances

Fainting spells, erectile dysfunction, night sweats, gastric or digestive disturbances, hypotension, dry mouth, palpitations, disturbed skin temperature profiles and abnormal pupillary function have all been described in association with narcolepsy but not systematically studied[205]. Finally, patients with narcolepsy also have increased rates of olfactory dysfunction, headache and chronic lower back pain. The origin and relevance of these features to the diagnosis of narcolepsy remain unclear at this point[174,206–208].

Clinical features in children

The first symptoms of narcolepsy in children are often weight gain and EDS. Sleepiness in children can lead to longer sleep times than in adults because nocturnal sleep can be normal in children even in the presence of severe EDS and cataplexy. Children fighting against EDS might also appear restless and hyperactive. Cataplexy episodes occurring soon after symptom onset are characterized by a mixture of negative (facial atonia with ptosis, mouth opening and tongue protrusion) and positive (perioral movements, dyskinetic–dystonic movements and stereotypies) motor phenomena that fluctuate with emotions[137]. These motor phenomena (termed facies cataplectica) tend to improve over time and can even disappear[28]. Occasionally, children present from symptom onset with hallucinations, sleep paralysis, disrupted sleep and even RBD. Other manifestations of childhood narcolepsy with cataplexy include


a
b
Sudden positive emotions
Medial prefrontal cortex
Central amygdala
Orexin
Reduced activity in ventrolateral periaqueductal grey area
Increased activity in sublaterodorsal tegmental nucleus
Increased inhibition of motor neurons
Cataplexy
c
Cataplexy attack
EOG 1
EOG 2
Chin-EMG
C3-A2
C4-A1
O1-A2
O2-A1
Tibial EMG r
Tibial EMG l

◀ Fig. 2 | **Cataplexy in patients with narcolepsy. a** | A cataplexy attack showing rapidly progressive bilateral loss of muscle tone and control of facial, neck and upper extremity muscles during laughter triggered by tickling. Consciousness is preserved, and muscle twitching or face grimacing can occur. **b** | Sudden, positive emotions activate neurons in the medial prefrontal cortex that excite orexin neurons in the lateral hypothalamus and the central amygdala. The absence of orexin leads to reduced activity of GABAergic neurons in the periaqueductal grey area that inhibit rapid eye movement (REM) sleep and increases the activity of glutamatergic neurons in the sublaterodorsal tegmental nucleus involved in REM atonia. The imbalance in this pathway results in the activation of descending pathways that inhibit spinal motor neurons and eventually to cataplexy. Pathways shown in blue are excitatory; those in red are inhibitory. Open circles indicate neuron-cell bodies. Dotted lines indicate reduced activity. **c** | An electromyography (EMG) recording during a cataplexy episode (shaded area) documents a loss of muscle tone in multiple channels with superimposed bursts of increased muscle phasic activity (which present clinically as motor phenomena such as muscle twitching and face grimacing). EOG, electro-oculography channel; l, left; r, right.

cognitive, behavioural and psychiatric disturbances, including depression, hyperactivity, aggression and psychosis[28,187,209]. Some children with narcolepsy and cataplexy undergo precocious puberty, which is associated with obesity[201].

Diagnosis

Patients with narcolepsy are often undiagnosed or misdiagnosed. The mean interval between symptom onset and diagnosis was found in a large-scale European study to be as long as 14 years[33]. Diagnosis of narcolepsy is often particularly difficult and delayed in children, in part because of their sometimes unusual presentations of EDS and cataplexy. In addition, no normative data exist for multiple sleep latency test (MSLT) findings in children, and experience with CSF orexin measurements in children aged <6 years is scarce.

Narcolepsy type 1

The current international classification of sleep disorders defines NT1 as the presence of EDS for >3 months in association with either CSF orexin levels <110 pg/ml (measured, however, using a method that has not been validated internationally) or cataplexy and a mean sleep latency <8 min on the MSLT and at least two SOREMPs during the MSLT and/or night-time polysomnography. NT1 is the most common and best understood form of narcolepsy.

A positive diagnosis of NT1 can be made on clinical grounds (BOX 1). EDS is often the presenting symptom; however, only cataplexy is pathognomonic for narcolepsy. Thus, correct identification of cataplexy is crucial. Cataplexy is, however, rarely observed and must be diagnosed by history: no validated tools exist, although a standardized trigger test might be useful[210]. Few papers support the utility of videographic and neurophysiological documentation of cataplexy[130,136].

Narcolepsy type 2

In the current international classification of sleep disorders, NT2 is defined as the presence of EDS for >3 months in the absence of cataplexy, but with a mean sleep latency on the MSLT <8 min and ≤2 SOREMPs on the MSLT and/or nocturnal polysomnography, as well as CSF orexin levels >110 pg/ml (or not measured). If cataplexy develops over time or CSF orexin levels decrease to <110 pg/ml, the diagnosis of NT2 must be changed to NT1.

Compared with patients with NT1, individuals with NT2 have less-severe EDS and a lower frequency of REM sleep-related symptoms, such as sleep paralysis, hallucinations and RBD[211]. Nonetheless, NT2 remains a controversial entity. This uncertainty persists partly because NT2 is a diagnosis of exclusion, meaning that other reasons for the patient's symptoms (such as chronic sleep loss or deprivation, sleep apnoea, circadian rhythm disorders and medication and/or substance abuse) must be excluded by ancillary tests. However, the existence of NT2 is supported by several observations. First, cataplexy generally does develop in patients with initially isolated EDS — usually after some weeks, although the interval can last several decades. Second, some degree of orexin loss is evident in the brains of patients who have narcolepsy without cataplexy[62]. Third, animal models of partial orexin loss exhibit EDS but not cataplexy[212].

Drawbacks of current criteria

The current international classification criteria have been criticized because they overemphasize the value of ancillary findings that are either nonspecific (SOREMPs) or not sufficiently validated (although orexin deficiency is a well validated biomarker of narcolepsy, current tools for measuring CSF orexin levels exhibit some methodological issues[213–215] and might also detect inauthentic orexin metabolites[216]). In addition, they do not provide validated (operational) definitions for the diagnosis of cataplexy and do not take into account the existence of different phenotypes and aetiologies of narcolepsy. HLA-DQB1*06:02 positivity, SOREMPs and low CSF orexin levels can also be observed in patients with partial or atypical or even without any clinical features of narcolepsy[56,217,218]. The authors of this Review suggest that the current criteria for narcolepsy require revision (and are preparing a paper presenting their views). The future classification of narcolepsy should take into account its different clinical and aetiological phenotypes (TABLES 1, 2).

Narcolepsy phenotypes. From a clinical standpoint, several possible phenotypes of narcolepsy can be identified: narcolepsy with typical (unequivocal) cataplexy and with all biological markers (namely, HLA-DQB1*06:02 positivity, sleep-onset REM episodes and low or absent CSF levels of orexin A); narcolepsy with typical cataplexy but without any biological markers; narcolepsy without cataplexy but with some biological markers; and the presence of some biomarkers in the absence of narcolepsy symptoms[36,62].

Narcolepsy with typical cataplexy and with all typical biological markers can initially present as narcolepsy without cataplexy and with normal CSF levels of orexin A. Narcolepsy with typical cataplexy but without any biological markers is often familial or secondary narcolepsy. Finally, narcolepsy without cataplexy but with some biological markers can evolve (within months but also after years) into NT1. Familial and secondary forms of narcolepsy seem to be particularly likely to present as absence of HLA-DQB1*06:02 positivity and normal orexin levels, although the exact frequency of this

Table 1 | **Clinical phenotypes of narcolepsy**

Clinical phenotypes	Proportion of cases (%)
Narcolepsy with typical cataplexy and with all typical biological markers (HLA DQB1*06:02, sleep onset rapid eye movement sleep episodes, low or absent cerebrospinal fluid levels of orexin A)	50–80
Narcolepsy with typical cataplexy but without all typical biological markers (often familial or secondary narcolepsy)	5–10
Narcolepsy without cataplexy but with some typical biological markers	18–34

phenotype is unknown. Lack of HLA-DQB1*06:02 positivity and orexin deficiency are rarely observed in patients with narcolepsy and cataplexy but are not infrequent in patients with atypical symptoms or rare forms of the disease or without cataplexy[33,219].

The existence of narcolepsy without cataplexy and without SOREMPs (so-called non-REM narcolepsy) is controversial[220,221]. Accordingly, current diagnostic criteria do not recognize this disease entity as a form of narcolepsy and do not differentiate it from idiopathic hypersomnia (except for one subtype of idiopathic hypersomnia that is associated with prolonged sleep time and 'sleep drunkenness')[220,222].

Narcolepsy aetiologies. From an aetiological standpoint, four forms of narcolepsy can be differentiated: sporadic idiopathic narcolepsy, familial narcolepsy, sporadic secondary narcolepsy (attributable to brain damage and other diseases)[52] and hereditary secondary narcolepsy ('narcolepsy-plus' syndromes)[223,224] (TABLE 2).

Sporadic secondary narcolepsy is most commonly caused by focal lesions in the hypothalamus (for example, in neurosarcoidosis or neuromyelitis optica) and brainstem[110,224,226–231]. In hereditary narcolepsy syndromes, narcolepsy is associated with neurological deficits or disturbances such as deafness, cerebellar ataxia and polyneuropathy[223,224]. An association between narcolepsy and multifocal brain diseases (such as traumatic brain injury or multiple sclerosis) has also been reported[5,8,102,106]

Differential diagnosis

The presence of EDS within a few hours after awakening, involuntary napping during active situations and the characteristics of these naps (short-lasting, refreshing and with dream content) are features suggestive of narcolepsy[220]. Severe EDS and 'sleep attacks' can however occur in sleep disorders other than narcolepsy, such as idiopathic hypersomnia, chronic sleep deprivation or insufficiency and sleep-disordered breathing, and in individuals doing shift work[34,232]. Narcolepsy-like EDS can also be observed in patients with brain and psychiatric diseases[233,234]. On the other hand, severe EDS and sleep attacks can be misdiagnosed as epilepsy, syncope or transient loss of consciousness, blackouts or ADHD[190,235] (BOX 2).

Cataplexy must be differentiated from mild episodes of loss of muscle tone, which can occur in 5–10% of healthy individuals, particularly when laughing. These cataplexy-like episodes (colloquially termed being 'weak with laughter') are usually not visible and involve mainly the lower limbs, whereas genuine cataplexy is visible and involves the face (partial attacks) or the entire body (generalized cataplexy)[34,129,210,236–238]. Videographic recordings can be helpful to correctly distinguish cataplexy from cataplexy-like episodes[130] (BOX 2). Cataplectic attacks, often with atypical characteristics (long duration, asymmetric presentation, an unusual trigger or without associated EDS), can occur in patients with hereditary neuropaediatric syndromes (such as Prader–Willi syndrome, Niemann–Pick disease type C and Norrie disease), in individuals with brain lesions, most commonly in the hypothalamus or brainstem, and in patients with psychiatric diseases[48,52,225,240]. Of note, patients with narcolepsy can present with both typical and psychogenic cataplectic attacks (pseudocataplexy)[48,178]. Pseudocataplexy is characterized by atypical triggers, a long or variable duration of attacks, lack of facial involvement and the persistence of deep tendon reflexes during generalized attacks (these reflexes are absent in genuine generalized cataplexy)[48,130,178]. Cataplexy-like episodes have also been described in the context of gelastic seizures and hyperkalaemic periodic paralysis[241]. In a few patients, typical cataplexy can remain isolated (that is, in the absence of EDS) for decades[35,242]. Typical ('true') cataplexy can be misdiagnosed as syncope, transient loss of consciousness, blackouts, epilepsy, exaggerated startle or falls of unknown origin and even as a transient ischaemic attack or stroke[235,243–245] (BOX 2).

A high frequency of sleep paralysis and hallucinations (>3 per month) and their occurrence at sleep onset are suggestive of narcolepsy, but these symptoms also occur in healthy individuals and in patients with other sleep, neurological and psychiatric disorders[34,239,246–249] (BOX 2).

Table 2 | **Aetiological forms of narcolepsy**

Aetiological forms	Proportion of cases (%)
Sporadic narcolepsy	>90
Familial narcolepsy	<5
Secondary (symptomatic) narcolepsy	<5
Hereditary 'narcolepsy plus' syndromes	<1

Diagnostic tests

Sleep questionnaires, video polysomnography, MSLTs and orexin measurements are recommended by US guidelines to confirm the diagnosis of narcolepsy as defined by current international criteria[18]. However, some of these tests have limited sensitivity and specificity. Genetic testing for HLA-DQB1*06:02 positivity adds little to the reliability of the diagnosis of NT1; however, its absence makes the diagnosis of NT1 highly improbable. In patients with unclear clinical findings, therefore, genetic testing is helpful.

Questionnaires. Patients with narcolepsy usually score ~18 (range 14–20 out of a possible 24) points on the nonspecific Epworth sleepiness scale[33,34,250]. The Swiss Narcolepsy Scale was found to have the best sensitivity and specificity (both ~90%) for the diagnosis of narcolepsy with cataplexy in three separate populations and was also superior to the Ullanlinna Narcolepsy Scale[20,34,250,251].

Box 2 | **Differential diagnosis of narcoleptic symptoms**

Excessive daytime sleepiness

- Other sleep disorders: idiopathic hypersomnia, sleep deprivation and sleep-disordered breathing
- Neurological and psychiatric diseases: Parkinson disease, atypical depression, epilepsy and attention disorders
- Use of sedative or hypnotic agents, drugs or alcohol
- Syncope or transient loss of consciousness and blackouts can sometimes be misdiagnosed as 'sleep attacks' (and vice versa)

Cataplexy

- Mild cataplexy (in the legs and often face but not visible) occurs with laughter in healthy individuals (feeling 'weak with laughter')
- Cataplexy-like episodes and/or atypical cataplectic attacks can occur in the context of hereditary paediatric syndromes (including Niemann–Pick disease type C, Prader–Willi syndrome and Norrie disease), lesions in the hypothalamus or brainstem and psychiatric diseases (pseudocataplexy), gelastic seizures, and hyperkalaemic periodic paralysis
- Syncope or transient loss of consciousness, 'drop attacks', blackouts, startle and seizures can sometimes be misdiagnosed as cataplexy (and vice versa)

Sleep paralysis and hallucinations

- In healthy individuals
- In patients with other sleep, neurological and psychiatric diseases

Multiple sleep latency test. Typical findings of short sleep latency and SOREMPs (FIG. 1) have a sensitivity and specificity of only ~70–80% for NT1 and (as per the definition) of 100% for NT2. Of note, patients with NT2 had longer non-REM and REM sleep latency durations on the MSLT than did patients with NT1[211,219]. However, MSLT findings are influenced by age, shift work, sleep deprivation and medication[217,218,252,253]. The MSLT reveals ≥2 SOREMPs in 4–13% of healthy individuals in the general population, and ≤3–6% of this population fulfils the MSLT criteria for the diagnosis of narcolepsy[217,218,254,255]. The sequence of sleep stages might differentiate the different aetiologies of EDS better than sleep latency duration[256,257]. In patients with NT1, typical MSLT findings are also present at follow-up examinations, whereas in individuals without cataplexy, the MSLT findings frequently improve or SOREMPs disappear over time[37,218].

Video polysomnography. SOREMPs can be identified during nocturnal video polysomnography in ~50% of patients with NT1 (REFS[258,259]), and this test seems to be more specific but less sensitive than the MSLT for the diagnosis of narcolepsy. Other findings on video polysomnography in patients with narcolepsy include awakenings and/or arousals after sleep onset, an increased amount of stage 1 sleep, frequent shifts to N1 sleep or waking from deeper stages of sleep, insufficient non-REM sleep density, increased frequency of sleep-disordered breathing, minor motor events during REM sleep, RBD and periodic limb movements in sleep[147,154,155,158,260]. In toddlers and preschool children, continuous 24 h polysomnographic recordings are preferred to conventional nocturnal polysomnography and MSLT for the detection of EDS and SOREMPs.

Orexin levels. CSF levels of orexin A are either greatly decreased (<110 pg/ml) or undetectable in 95% of patients with NT1 (REFS[56,213]). This is the most sensitive and specific diagnostic test for NT1, although the radioimmunoassay currently used to measure orexin A levels gives only relative values, cannot quantify small changes and additionally might detect inauthentic orexin metabolites[216,261]. In patients without cataplexy, CSF orexin levels are usually normal (so-called NT2). However, some of these patients (10–25% in large series; range 0–40%) present with CSF levels of orexin A <110 pg/ml and are therefore diagnosed as having NT1 (REFS[36,213,261]). Normal CSF levels of orexin are often found in patients with familial and secondary narcolepsy and in HLA-DQB1*06:02-negative patients[36,213].

Neuroimaging. A variety of neuroimaging studies have been performed in patients with narcolepsy in the past 20 years. Older structural imaging modalities showed normal findings; however, reports published in the past 3–4 years, which used more-advanced techniques, suggest that the frequency of brain abnormalities (such as demyelinating and vascular changes) might have been underestimated[106,262,263]. The number of quantitative morphological, spectroscopic and metabolic imaging studies is limited, and their results often could not be replicated[49,264–268]. Functional MRI studies have provided new insights into the neuronal networks underlying human cataplexy by showing altered patterns of activity with laughter in the hypothalamus and cortico-limbic and brainstem reward pathways[269]. The documented abnormalities in reward and emotional processing observed in patients with narcolepsy might explain the high frequency of psychiatric disturbances in affected individuals[180,181,270,271].

Pathophysiology

In the 1920s, observations in patients with encephalitis lethargica led to the suggestion that narcolepsy originates from the diencephalon and of its role in sleep generation and the control of muscle tone[8,40,92]. The discovery of SOREMPs in 1960, together with other neurophysiological and biochemical observations in humans and dog models of narcolepsy, led to the proposal that narcolepsy results from an imbalance of aminergic and cholinergic brainstem pathways[14,272,273], as discussed in this section.

Neurochemistry

Orexin. Orexin-producing neurons regulate sleep–wake behaviour and influence other brain functions, including reward and metabolic circuits, through their effects on numerous targets, including neurons producing histamine and other monoamine neurotransmitters[274–277]. Orexin-producing neurons are most active during wakefulness, especially during periods of high muscle tone and in motivated and exploratory behaviours, and they help to sustain long periods of wakefulness and regulate REM sleep[278].

Narcolepsy was first linked to reduced orexin signalling when researchers observed narcolepsy phenotypes in mice lacking orexin neuropeptides and in dogs with mutations in *HCRTR2* (which encodes orexin receptor type 2)[279,280]. Soon afterwards, researchers demonstrated low orexin levels and loss of orexin-producing

neurons in ~90% of patients who had NT1 or narcolepsy with cataplexy[17].

The specific mechanisms through which loss of orexin signalling results in EDS and cataplexy are still being established, but signalling through monoamine neurons seems to be important: in mice, restoration of orexin signalling in the noradrenergic neurons of the locus coeruleus improves EDS, and restoration of orexin receptor expression in the serotoninergic neurons of the dorsal raphe improves cataplexy[281]. Also in mice, intracerebroventricular and intrathecal injections of orexin and orexin agonists inhibit cataplexy[282,283].

The severity of sleepiness and cataplexy seem to be correlated with the extent of orexin neuron loss and with the decrease in CSF levels of orexin[62,65]. Loss of orexin neurons to below 50% of normal levels is found in patients with NT2 and corresponding rodent models[62,284]. Symptoms in patients with NT2 might arise from orexin loss but also other compensatory mechanisms. Of note, low levels of orexin in CSF in these patients predicted the subsequent development of cataplexy[36].

Histamine. Histaminergic neurons of the posterior hypothalamus are another major target of the orexin system. Histaminergic neuron firing and histamine release are maximal during wakefulness, and wakefulness is diminished by the destruction of histaminergic neurons and by inhibition of histamine synthesis, release or action[285]. In humans, CSF levels of histamine and its main metabolite can be low in patients with narcolepsy[286–289], but this finding is controversial because it remains unclear whether these changes represent compensation for the loss of orexin neurons or are related to the underlying autoimmune or inflammatory process. Finally, pitolisant, a selective histamine H3 receptor inverse agonist, improves wakefulness and reduces cataplexy in mice and people with narcolepsy[290].

Other neurotransmitters. Orexin neurons also produce glutamate, neuronal activity-regulated pentraxin and the endogenous opiate dynorphin[45,57]. Their role in narcolepsy remains unclear. A few studies have also suggested a link between narcolepsy and lipocalin-type prostaglandin D synthase (also known as prostaglandin H_2 D-isomerase), an enzyme involved in sleep–wake regulation in rodents, primates and humans[291–293].

Neurophysiology

Excessive daytime sleepiness. Orexin neurons heavily innervate and excite all brain regions that promote arousal, including noradrenergic neurons of the locus coeruleus, dopaminergic neurons of the ventral tegmental area, histaminergic neurons of the tuberomammillary nucleus and cholinergic neurons of the basal forebrain[294] (FIG. 1). In contrast to classic short-acting neurotransmitters, orexins persistently excite their target neurons; intraventricular injection of orexin A or administration of an orexin agonist increases wakefulness for several hours in mice[282]. However, the loss of orexin-producing neurons in patients with narcolepsy probably means that these wakefulness-promoting neurons fire less consistently, resulting in EDS and rapid transitions into sleep. Low CSF levels of orexin A predict an increased severity of EDS in people with narcolepsy[36,211].

Cataplexy and rapid eye movement sleep symptoms. During REM sleep, motor neurons are hyperpolarized by inhibitory interneurons (which produce GABA and glycine) in the spinal cord and by descending projections from the medial medulla (FIG. 2). These atonia-promoting neurons are activated by glutamatergic neurons of the sublaterodorsal nucleus[295]. During wakefulness and non-REM sleep, these sublaterodorsal nucleus neurons are normally inhibited by neurons of the ventrolateral periaqueductal grey area and the adjacent lateral pontine tegmentum as well as by serotoninergic neurons of the dorsal raphe[296]. During normal REM sleep, these neurons fall silent, permitting widespread muscle paralysis[296]. Cataplexy can, therefore, be viewed as an altered startle response accompanied by an inappropriate activation (that is, during wakefulness) of the pathways that normally produce muscle paralysis during REM sleep. However, these two phenomena, cataplexy and REM atonia, are neither clinically nor physiologically (nor indeed pharmacologically) identical[272,297–299]. Sleep paralysis and hallucinations probably also arise from a dysregulation of REM sleep[300,301]. Accordingly, these symptoms in patients with narcolepsy are often referred to (together with cataplexy and RBD) as REM sleep manifestations.

We are beginning to understand how strong, positive emotions trigger cataplexy. Functional MRI studies suggest that people with narcolepsy have altered patterns of activity with laughter in the hypothalamus and the cortico-limbic and brainstem reward pathways[180,269,270]. The amygdala also contains neurons that are active during cataplexy; in mice lacking orexins, selective activation of GABAergic neurons in the central nucleus of the amygdala increases the severity of cataplexy, whereas their selective inactivation reduces it[302–304]. These amygdala neurons heavily innervate the ventrolateral periaqueductal grey area, lateral pontine tegmentum and dorsal raphe, and this inhibitory signal is likely to inhibit atonia-suppressing brain regions, enabling transitions into cataplexy. In line with this suggestion, lesions in the central and basolateral nuclei of the amygdala reduce cataplexy in a mouse model of narcolepsy[305]. Studies in patients with narcolepsy also suggest that they have alterations not only in patterns of activation of the amygdala during cataplexy but also in emotional processing, including of positive, aversive and negative emotions[181,269,306–308]. In healthy individuals, orexins excite the ventrolateral periaqueductal grey area and the adjacent lateral pontine tegmentum and dorsal raphe, counterbalancing these inhibitory signals from the amygdala, but in individuals with narcolepsy, the signals from the amygdala are unopposed, resulting in cataplexy.

Further upstream, the medial prefrontal cortex is a major input to the amygdala, and it is active in association with positive emotions and cataplexy in humans[269]. In mice lacking orexins, this region shows highly synchronous firing during cataplexy; inhibition of the medial prefrontal cortex in these mice reduced cataplexy[309,310].

In EEG studies, the presence of hypersynchronous theta oscillations during cataplexy episodes in rodents and humans might reflect changes in prefrontal control of reward-driven motor impulse, planning and conflict monitoring[310].

Treatment

Patients with narcolepsy require counselling (for example, for school-related and work-related issues), psychosocial guidance and regular medical follow-up. Non-pharmacological approaches should always be discussed. Age, profession, specific life situations (such as pregnancy) and comorbidities (including depression, obesity, cardiovascular disorders, restless legs syndrome, periodic limb movements, RBD and sleep-disordered breathing) all influence the choice of treatment but have been insufficiently studied. Sleep propensity can be assessed using the same questionnaires and sleep–wake tools (such as the Epworth sleepiness scale and maintenance of wakefulness test, respectively) that are used to assess treatment response in clinical trials. New tools that assess the quality of wakefulness and patients' overall quality of life are increasingly also being used[311,312].

Non-pharmacological approaches

Non-pharmacological treatment strategies include self-care, behavioural therapy (including scheduled napping and regular night sleep), self-help groups and psychotherapy. Regular physical activity, adequate use of caffeine and a balanced diet that avoids large amounts of carbohydrates are also recommended[313].

Symptomatic pharmacological approaches

Pharmacological treatments for narcolepsy (TABLE 3) add to but do not replace non-pharmacological therapies. In many patients, optimal control is possible only with a combination of pharmacological and non-pharmacological approaches.

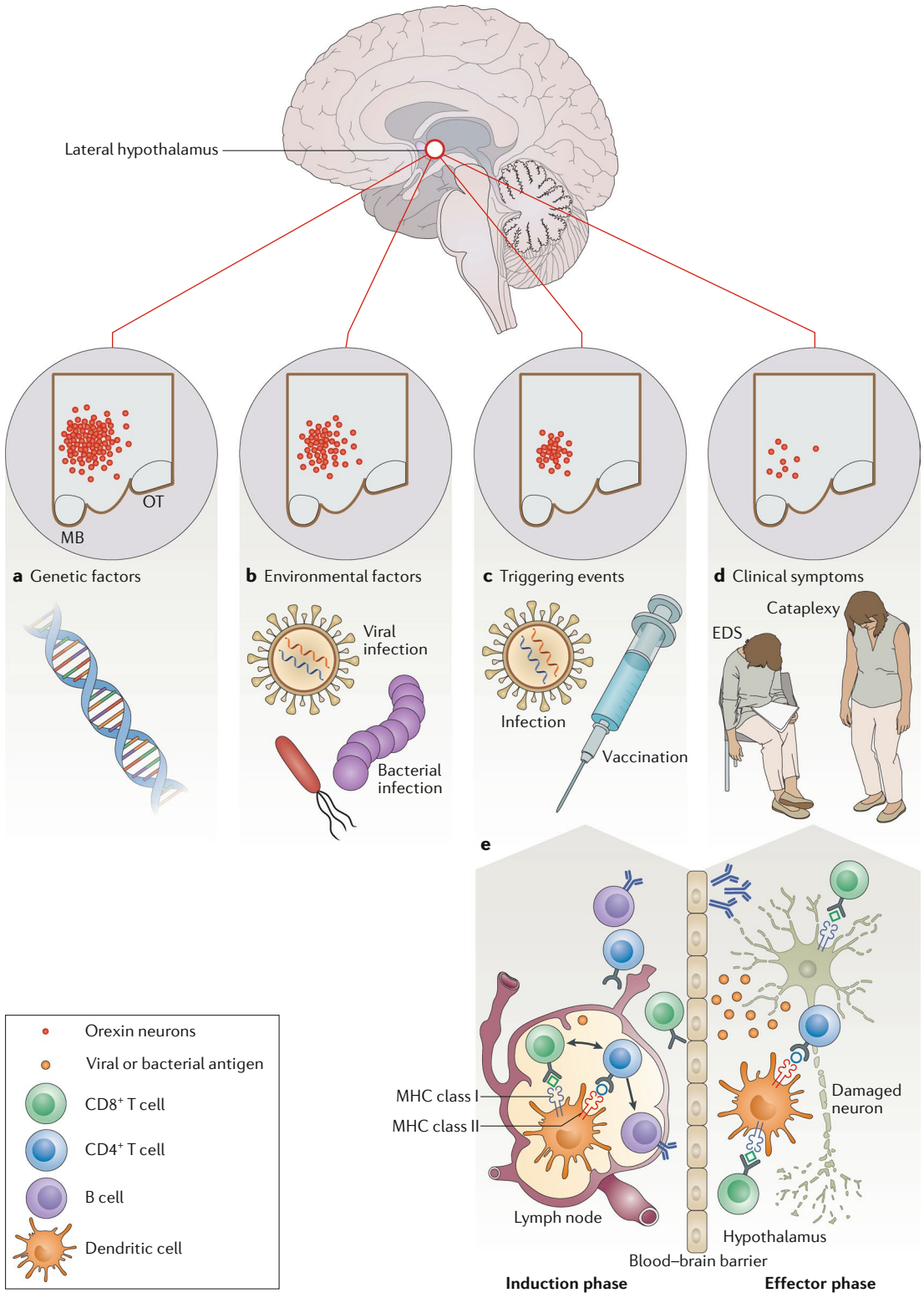
Coffee, ephedrine and benzedrine in the 1930s and methylphenidate in the 1950s were the earliest treatments for narcolepsy[8,314]. The anticataplectic effects of imipramine, clomipramine and other antidepressants were initially reported in Japan[315]. In humans, drugs that increase noradrenergic and serotoninergic tone, such as the selective noradrenaline reuptake inhibitor venlafaxine and the selective serotonin reuptake inhibitor fluoxetine, are effective in reducing the severity of cataplexy[281,316,317]. The efficacy of sodium oxybate (the sodium salt of γ-hydroxybutyric acid) as a treatment for both EDS and cataplexy has been confirmed in double-blind randomized controlled trials[318–321]. Pitolisant (an inverse agonist of histamine) is also effective in the treatment of both EDS and cataplexy[322,323]. Codeine and opiates, which increased the number of orexin-producing cells detected in human and mouse brains and reversed cataplexy in a rodent model of narcolepsy, might have a symptomatic effect[324–326]. Additional drugs are currently in the pipeline, including small-molecule oral orexin agonists (which, unlike orexin itself, can pass through the blood–brain barrier)[281,317].

Excessive daytime sleepiness. Modafinil is a racemic compound, the active *R*-enantiomer of which, armodafinil, has a longer half-life. Both agents promote

Table 3 | **Symptomatic narcolepsy treatment**

Drug	Daily dosage	Indication	Approval status
Modafinil	100–400 mg	First-line treatment for EDS	Approved by FDA and EMA for NT1 and NT2
Armodafinil	100–250 mg	First-line treatment for EDS	Approved by FDA for NT1 and NT2; not available in Europe
Pitolisant	4.5–36.0 mg	First-line treatment for EDS and cataplexy	• Approved by EMA for NT1 and NT2 • Under review by FDA[a]
Sodium oxybate	4.5–9.0 g	First-line treatment for cataplexy, disturbed night-time sleep and EDS	• Approved by FDA for NT1 and NT2 • Approved by EMA for NT1
Solriamfetol	75–150 mg	First-line treatment for EDS	• Approved by FDA for NT1 and NT2 • Under review by EMA
Antidepressants	• Venlafaxine 37.5–300.0 mg • Fluoxetine 20–60 mg • Clomipramine 10–50 mg • Citalopram 10–75 mg	First-line and second-line treatment for cataplexy and third-line treatment for EDS	Clomipramine is approved in Germany for the treatment of cataplexy
Methylphenidate	10–60 mg	Second-line treatment for EDS	Approved by FDA and EMA for NT1 and NT2 (EMA approved immediate-release formulation only for NT1)
Amphetamines	• Amphetamine mixed salts[b] 10–60 mg • Dexamphetamine 10–60 mg	Second-line treatment for EDS	• Amphetamine mixed salts[b] are approved by the FDA for NT1 and NT2 • In Europe, dexamphetamine is approved in Germany and Switzerland

These recommendations apply only to adults. The presence of comorbidities (and other medications) might also alter the choice of pharmacological approach. EDS, excessive daytime sleepiness; EMA, European Medicines Agency; NT1, narcolepsy type 1 (with cataplexy or a proven cerebrospinal fluid orexin deficiency); NT2, narcolepsy type 2 (without cataplexy). [a]Designated as a breakthrough therapy for cataplexy and fast-tracked as a treatment for EDS and cataplexy in patients with narcolepsy. [b]A mixture of four salts of the two enantiomers of amphetamine with dexamphetamine.



dopaminergic signal transmission. Modafinil is approved by the European Medicines Agency (EMA), and both modafinil and armodafinil are approved by the FDA as a first-line treatment for EDS. These agents are effective within days[317,327,328]. Sodium oxybate is given at night and has a complex mode of action that includes the stimulation of GABA-B receptors. Pitolisant is approved by the EMA as a first-line treatment for EDS. The EMA has approved sodium oxybate for the treatment of narcolepsy with cataplexy[317,322]. Sodium oxybate might be the preferred option for patients with cataplexy, disturbed nocturnal sleep and EDS, although its maximal effect is reached only after ~3 months[329]. Solriamfetol is a selective dopamine and noradrenaline reuptake inhibitor for which favourable results have been reported in phase IIb and phase III trials; in 2019, this agent was approved

◀ Fig. 3 | **The multiple-hit model of narcolepsy involves genetic, environmental and triggering factors. a** | Genetic factors (especially HLA-DQB1*06:02 positivity) are a strong predisposition to narcolepsy. The first clinical marker of such a predisposition is a short latency period before onset of rapid eye movement (REM) sleep. **b** | Environmental exposures to bacterial and viral infections in early life might alter immune system development and predispose individuals to narcolepsy later in life. It is possible, but still unproven, that these changes might directly or indirectly cause the loss of some orexin neurons (as suggested in this figure). Alternatively, these genetic and environmental factors might only increase the vulnerability of these neurons. **c** | Triggering events, such as vaccinations and infections by viruses such as influenza type A (H1N1) and bacteria such as *Streptococcus* spp., induce or reactivate the immune response, leading to the destruction of orexin neurons (induction phase). **d** | The clinical symptoms of narcolepsy progress over days to weeks and even years, as an increasing number of orexin neurons is destroyed or silenced, causing an imbalance in brainstem sleep and wake pathways (effector phase) that leads to full-blown narcolepsy with cataplexy. **e** | The exact sequence of events leading to the selective destruction of orexin neurons in the hypothalamus is still unknown, but inflammatory cytokines and activated immune cells (dendritic cells, antigen-specific $CD4^+$ T cells and cytotoxic $CD8^+$ T cells), which eventually cross the blood–brain barrier, are thought to be involved. Antibodies can cross a disrupted blood–brain barrier and might also contribute to neuronal destruction. EDS, excessive daytime sleepiness; MB, mammillary body; OT, optic tract.

by the FDA for the treatment of EDS in patients with narcolepsy[330,331].

A second-line approved drug for EDS is methylphenidate. Amphetamine mixed salts (mixtures of four salts of the two enantiomers of amphetamine) and dexamphetamine are third-line choices that are approved only in some countries[317,332]. Mazindol (which is currently withdrawn from the market), selegiline, and to a lesser extent venlafaxine, have been used off-label in patients with EDS.

Cataplexy. Sodium oxybate is approved by the EMA and FDA as a first-line treatment for cataplexy[317,328]. The maximal effect of this agent is reached after ~3–6 months[329]. Low-dose clomipramine and low-dose imipramine, as well as venlafaxine, fluoxetine and other selective serotonin reuptake inhibitors can improve cataplexy within days but are not approved (in most countries) for this indication[317,333]. Pitolisant is also effective against cataplexy (class I evidence) and has been approved by the EMA[323]. A network meta-analysis of 14 randomized controlled trials in patients with narcolepsy found that modafinil 200–400 mg daily in patients with EDS, sodium oxybate 9 g daily in patients with EDS and cataplexy and pitolisant 40 mg daily in patients with EDS and cataplexy were all considerably more effective than placebo[334].

Other symptoms. Sodium oxybate is the only substance with a proven long-term benefit on nocturnal sleep[335]. Sodium oxybate, clomipramine and venlafaxine can improve hallucinations. Sodium oxybate might worsen sleep-disordered breathing. Antidepressants can worsen both RBD and restless legs syndrome[317].

Treatment of narcolepsy in children. Stimulants, modafinil, sodium oxybate and antidepressants improve narcoleptic symptoms in children. The clinical efficacy of sodium oxybate for the treatment of EDS and cataplexy was reported in 2018 in a large study conducted in children[336]. Sodium oxybate has been approved by the FDA for the treatment for narcolepsy with EDS and cataplexy in children. No other drugs are approved by either the EMA or FDA for use in children.

Special considerations. Although combined treatments are commonly used to treat EDS and cataplexy in adults, little formal evidence supports such an approach. Concurrent administration of modafinil and sodium oxalate or pitolisant might have additive effects on EDS[317]. The effects of stimulants on cognitive disturbances have been poorly studied. Sodium oxybate can improve obesity but might induce or worsen depression; the opposite effects are observed with antidepressants.

During pregnancy, delivery and breastfeeding (which probably do not differ much in women with narcolepsy from those in the general population), all drugs for EDS and cataplexy should be discontinued, if possible[337]. In some specific individuals with severe symptoms, low-dose clomipramine and/or modafinil might exceptionally be prescribed; in data on hundreds of pregnancies, these drugs seem to be safe[337,338].

Immunotherapy

Immunomodulatory treatments (including intravenous immunoglobulins, humanized monoclonal antibodies, high-dose corticosteroid therapy and plasmapheresis) have been investigated in small studies, with some success[39,112,113,339,340]. Natalizumab and alemtuzumab have also shown some beneficial effects on EDS or cataplexy in single patients[106,341].

Conclusions and future perspectives

The clinical observations and research triggered by the discovery of the orexin system in the late 1990s have greatly increased our knowledge of the clinical features and neurobiology of narcolepsy. However, a few important issues remain unclear. Six major areas of uncertainty need to be addressed in the near future, discussed below.

Narcolepsy is a rare disease. However, its exact incidence and prevalence remain unknown owing to the inadequacy of current diagnostic criteria. The frequency of narcolepsy and narcoleptic borderland conditions (including NT2) could be higher than currently suggested[218].

In the clinic, narcolepsy should be considered as a global hypothalamic disorder rather than simply as a sleep disorder. In addition to sleepiness and sleep disorders, patients with narcolepsy manifest various other motor, cognitive, psychiatric, emotional, metabolic and autonomic disturbances. Although these disturbances are still insufficiently characterized and poorly understood, they probably reflect an underlying hypothalamic dysfunction in orexin signalling and connected neuronal networks. Prospective and long-term clinical observations are needed to increase our knowledge of the different forms of narcolepsy in terms of both their natural history and evolution (that is, acute versus chronic or progressive) and their severity (which ranges from mild narcolepsy without cataplexy to severe narcolepsy with cataplexy). These differences are suggestive of a multiple-hit aetiopathogenesis of narcolepsy (FIG. 3).

Narcolepsy arises from the contribution of well-identified genetic polymorphisms, still poorly characterized environmental exposures and possibly epigenetic factors. The extent (and nature) of these aetiological contributions probably differs between idiopathic, familial and secondary variants of the disease. Systematic assessments, including neuroimaging studies and measurements of inflammatory markers (such as cytokines and $CD8^+$ and $CD4^+$ lymphocytes), and comorbidities of narcolepsy might shed light on potential disease-triggering or disease-modifying factors. Emerging evidence, gained in humans and rodent models of the disease, supports the recruitment of immunological mechanisms in the destruction or silencing of orexin neurons[94,342,343]. If confirmed, this information will have profound consequences because it would enable the early diagnosis of incomplete phenotypes, the selection of appropriate treatment (symptomatic versus immunomodulatory) and perhaps even the prevention of narcolepsy in predisposed individuals.

Orexin deficiency is central to the pathophysiology of narcolepsy, although the exact underlying mechanisms are still incompletely understood[303]. In addition, human as well as animal data suggest that other neurotransmitters (such as histamine[66]) are dysregulated in narcolepsy. The extent of such dysregulation, and whether it is a primary or secondary (that is, downstream or compensatory) effect of the disease, remains unclear but could be of interest for the development of new diagnostic and treatment strategies.

The current diagnostic criteria for narcolepsy are imprecise, particularly those for the identification of cataplexy and the exclusion of narcolepsy mimics. They are also cumbersome to apply and do not adequately reflect the existence of different clinical phenotypes and aetiologies of narcolepsy. These criteria should be revised using a scale for diagnostic probability of narcolepsy (possible, probable certain or certain diagnosis). The diagnosis of cataplexy remains difficult: cataplexy-eliciting tests and videographic analyses, which are well established in animal models, have only rarely been systematically used in humans[130,210,344]. Simpler methods than the MLST are also needed to increase the diagnostic sensitivity and specificity of assessing neurophysiological sleep–wake changes, including sequencing of sleep stages, in patients with narcolepsy and narcolepsy-like phenotypes[259,345]. More-precise quantitative methods than the existing radioimmunoassay are needed to assess orexin deficiency in CSF and possibly also in serum and might lead to an improvement in the early and accurate diagnosis of mild forms of narcolepsy, including narcolepsy without cataplexy but with (presumably) normal CSF orexin levels[261,346]. Systems biology approaches, such as genomic, transcriptomic, epigenomic, proteomic and microbiomic analyses, are needed to identify new biomarkers of narcolepsy and borderland conditions. Machine-learning approaches might also improve on the accuracy of current diagnostic methods[219,345,347]. Blood tests for immune markers might also have a diagnostic role in the future[58]. Finally, knowledge and awareness of narcolepsy could be improved among physicians and in the general population[348].

The symptomatic treatment of narcolepsy has advanced considerably owing to the introduction of effective drugs approved by the EMA and FDA. However, compliance with treatment is not always sufficient. Also, the measurements of treatment efficacy currently used in clinical trials correlate poorly with narcolepsy-relevant outcome measures. New disease severity scales, vigilance tests, disease-specific measures of quality of life and patient-reported outcomes are needed[349–351]. Further clinical trials are also needed to investigate pharmacological treatments for narcolepsy in children and in other groups requiring special consideration (such as pregnant women and patients who have narcolepsy without cataplexy and in the perioperative period). Non-pharmacological approaches, including the role of napping and diet, should also be studied in clinical trials[336]. Treatment of comorbidities is often neglected but can be very important in some patients.

Orexin-producing cell replacement, gene and stem cell treatments and the use of orexin agonists are still experimental[282]. Conversely, immunomodulatory treatments (which address the causative mechanisms of narcolepsy) have been effective in single individuals and in small series of patients and could be considered in the future — if the autoimmune hypothesis of narcolepsy is confirmed — particularly in individuals in the early stages of NT1 and in those with progressive narcolepsy or NT2 (REFS[317,342]).

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Competing interests
C.L.A.B. declares that he is a member of the advisory boards of Idorsia, Jazz, Takeda and UCB. R.K. and M.T. declare that they are members of the advisory board of UCB. G.J.L. and G.M. declare that they are members of the advisory boards of Bioproject and UCB. T.S. declares that he is a member of the advisory board of Jazz. Y.D. declares that he is a member of the advisory boards of Bioproject, Harmony Biosciences, Idorsia, Jazz, Takeda and UCB. R.L. has received a research grant from GSK. UK declares that he is a member of the advisory boards of AOP Orphan Pharmaceuticals, Bioprojet, Harmony Biosciences, Jazz, and UCB. T.E.S. has received research grant support from Takeda and Merck. T.E.S. declares that he is a member of the advisory board of Avadel, Harmony Biosciences, Idorsia, Jazz and Takeda. The other authors declare no competing interests.

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