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REVIEW ARTICLE

Narcolepsy

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Summary

This article addresses the clinical presentation, diagnosis, pathophysiology and management of narcolepsy type 1 and 2, with a focus on recent findings. A low level of hypocretin-1/orexin-A in the cerebrospinal fluid is sufficient to diagnose narcolepsy type 1, being a highly specific and sensitive biomarker, and the irreversible loss of hypocretin neurons is responsible for the main symptoms of the disease: sleepiness, cataplexy, sleep-related hallucinations and paralysis, and disrupted nocturnal sleep. The process responsible for the destruction of hypocretin neurons is highly suspected to be autoimmune, or dysimmune. Over the last two decades, remarkable progress has been made for the understanding of these mechanisms that were made possible with the development of new techniques. Conversely, narcolepsy type 2 is a less well-defined disorder, with a variable phenotype and evolution, and few reliable biomarkers discovered so far. There is a dearth of knowledge about this disorder, and its aetiology remains unclear and needs to be further explored. Treatment of narcolepsy is still nowadays only symptomatic, targeting sleepiness, cataplexy and disrupted nocturnal sleep. However, new psychostimulants have been recently developed, and the upcoming arrival of non-peptide hypocretin receptor-2 agonists should be a revolution in the management of this rare sleep disease, and maybe also for disorders beyond narcolepsy.

KEYWORDS
narcolepsy type 1, narcolepsy type 2, orexin/hypocretin, pathophysiology, treatment

1 | INTRODUCTION

Narcolepsy is a rare sleep disease, but probably one of the most studied and best understood sleep disorders from a pathophysiological point of view, being a model of severe sleepiness of neurological origin. Narcolepsy was first described in the late 19th century by three European researchers: Westphal, Gélineau and Fischer (Fisher, 1878; Gélineau, 1880; Westphal, 1877). By 1924, only 35 patients had been reported in the literature, but the breakthrough discovery of orexin-A and B/hypocretin-1 and 2 (Hcrt) as new neuropeptides in 1998 (de Lecea et al., 1998; Sakurai et al., 1998), and their implication in the pathophysiology of narcolepsy in 2000 (Peyron et al., 2000; Thannickal, 2000), lead to an increased interest in this rare but fascinating disorder. Over the past decades, considerable progress has been made in our understanding of the aetiology, description of the phenotype, clinical and electrophysiological features, comorbidities, and management of this disease. This article synthesizes these extraordinary advances in the field, providing an overview of former and recent findings. Narcolepsy type 1 (NT1), with low–undetectable cerebrospinal fluid (CSF) Hcrt-1 levels, formerly named narcolepsy with cataplexy, is characterized by a pentad of symptoms: excessive daytime sleepiness (EDS), cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations, and disrupted nocturnal sleep (DNS) (AASM: American Academy of Sleep Medicine, 2014). Narcolepsy type 2 (NT2), with normal CSF Hcrt-1 levels, shares most clinical features with NT1, except cataplexy, but is probably more heterogeneous, and currently less well defined. These rare central disorders of hypersomnolence need to be further explored (Dauvilliers & Barateau, 2017).

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2 | CLINICAL FEATURES

2.1 | Excessive daytime sleepiness

The predominant and most disabling symptom of narcolepsy is EDS. EDS is often the first symptom to appear, starting suddenly after a triggering environmental factor, but it can sometimes develop gradually. Sleepiness occurs daily, typically during inactivity, but also at work, at school, and while driving. Sleep episodes are irresistible, of short duration, sometimes real sleep attacks, and often associated with dreaming, because of a premature occurrence of rapid eye movement (REM) sleep (Dauvilliers et al., 2003b). Narcoleptic patients usually feel refreshed after a short nap, but sleepiness returns soon later. They do not have an excessive amount of sleep over the 24-hr period, but rather fragmented wakefulness and sleep periods ("sleep and wake bouts"), being unable to stay awake or asleep for a long time. The severity of EDS can vary from a patient to another. In the most severe cases, episodes of irresistible sleep attacks, or unconscious lapses occur while talking to someone, or even when eating or driving, making this symptom socially disabling or even dangerous. EDS can lead to deficits in work performance, social impairment, and car, work or machine accidents (Pizza et al., 2015a). EDS is often less severe in NT2 than in NT1. Patients, and especially children, can also experience automatic behaviours during daytime, with continuation of activity with no memory of the event, in a conversation, or writing automatically off the topic (Dauvilliers et al., 2007a). Paediatric narcolepsy can present a distinct phenotype, as children often manifest sleepiness with behavioural changes such as hyperactivity, irritability and attention deficits (attention deficit hyperactivity disorder; ADHD).

2.2 | Cataplexy

This symptom is pathognomonic of NT1. A cataplectic attack is a sudden and involuntary loss of muscle tone while awake, with a sparing of the muscles associated with breathing (Dauvilliers et al., 2014). It is triggered by strong emotions, often positive, such as laughing, being surprised, meeting a friend, or telling a joke. Intense negative emotions such as anger are rare, and cataplexy is almost never triggered by fear or stress (Overeem et al., 2011; Sturzenegger & Bassetti, 2004). This phenomenon is one of the best diagnostic markers of NT1, but it has a large inter-variability in phenotype, duration, frequency and severity (Dauvilliers et al., 2014). An episode can last a few seconds (or even 1 s) to a few minutes, and can happen once a year or several times a day. A cataplectic attack can be partial, with a preferential localization on facial and neck muscles resulting in head drop, but also dysarthria, jaw tremor, difficulties to smile. It can be limited to the upper or lower limbs, with the drop of objects or weakness of the knees. A cataplexy can also be generalized, with a complete atonia resulting in total collapse, but patients get rarely injured. A generalized cataplexy is accompanied by an abolition of deep-tendon reflexes and monosynaptic Hoffmann reflex activity, but we showed that deep-tendon reflexes persist in partial or mild episodes (Barateau et al., 2018b). In children the phenotype is different, especially when close to disease onset: negative and active motor disturbances are described, with subtle facial expressions or choreic-like movements, perioral movements such as grimacing and tongue protrusion (Plazzi et al., 2011). Interictal abnormal neurological examination with hypotonia and ataxic gait is also common. A lack of awareness of this symptomatology is not unusual, "cataplectic facies" and dyskinetic–dystonic movements or stereotypies being noticed and reported by parents but not by the child. Adults and children remain fully conscious during the episode. Some of them, however, report hypnagogic hallucinations, and rarely others can enter into REM sleep after a cataplexy. Cataplexy should be considered as differential diagnosis of episodic falls (Pillen et al., 2017), and recent data strongly suggest that video documentation of the event may be of help especially focusing on atonia-induced changes in the facial district also in adult patients (Pizza et al., 2018).

2.3 | Sleep paralysis, hypnagogic and hypnopompic hallucinations

Abnormal expressions of REM sleep, such as rapid transitions into REM sleep, sleep-related multisensory hallucinations (at the onset of sleep, hypnagogic; at awakening, hypnopompic) and sleep paralysis are described, but not specific of narcolepsy (Bassetti et al., 2019). These "intermediate states" are called REM sleep dysregulation, and express the dissociation between wakefulness and REM sleep at sleep onset/offset. Sleep paralysis occurs spontaneously on awakening from sleep, or when falling asleep, in half of the narcoleptic patients (Dauvilliers et al., 2007a; Sturzenegger & Bassetti, 2004). This inability to move the limbs, the head, or to speak and breath normally can be very frightening. Dreamlike auditory, visual or tactile hallucinations are common in narcolepsy, in about two-thirds of the patients, and lasting often less than 1 min. Those disturbing and sometimes scaring phenomenon can also occur, but occasionally, in 20% of the general population, but are more frequent and intense in narcolepsy (Ohayon, 2000).

2.4 | Disrupted nighttime sleep

The third most common symptom is DNS, after EDS and cataplexy, ranging from 30% to 95%, depending on the definition (Plazzi et al., 2008). A few years ago, international experts characterized DNS clinically and by polysomnography (PSG), and found that patients' description and PSG characterization are different from the typical features of insomnia (Morin et al., 2015; Roth et al., 2013). Patients experience fragmented nocturnal sleep, instability of wake and sleep, with inappropriate and sudden shifts between states (Pizza et al., 2015b; Plazzi et al., 2008).

The Hcrt system is known to stabilize sleep and wake regulation (Saper et al., 2005). A defect of the hypocretinergic tone may lead to this instability of behavioural states, with irresistible transitions into

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sleep and difficulty in maintaining long periods of wakefulness. We recently showed that DNS complaint is frequent in NT1, associated with disease severity, several PSG parameters and objective EDS; this symptom improved with treatment (Barateau et al., 2022). One study examined wake bouts measurements underlying the reduction of wake after sleep onset in patients with insomnia treated with a Hcrt-receptor antagonist (Svetnik et al., 2018), and we used a similar method to explore the relationships between CSF Hcrt-1 levels and markers of nocturnal sleep fragmentation assessed by PSG (wake bouts, sleep bouts and sleep/wake transitions) (Barateau et al., 2020b). We found that sleep and wake are reliable PSG markers of nighttime sleep stability, strongly correlated to CSF Hcrt-1 levels, with a dose–response effect. Those robust PSG biomarkers are promising to be used in clinical and research settings. In a recent study, an artificial intelligence algorithm could discriminate patients with NT1 by analysing their nocturnal sleep features only (Stephansen et al., 2018). The frequency and characteristics of DNS remain poorly defined and understudied in NT2, normal nocturnal sleep features being required for confirming diagnosis itself.

2.5 | Other sleep abnormalities and comorbidities

Narcolepsy type 1 is often associated with other sleep abnormalities (apnea, parasomnias, periodic legs movements [PLM], REM sleep deregulation), and also with a wide range of comorbidities such as neuropsychiatric disorders, obesity, metabolic, endocrine and autonomic disturbances. Nocturnal sleep in NT1 can be disrupted by many conditions, variably related to Hcrt deficiency. Motor control dysfunction with PLM (Dauvilliers et al., 2007b; Pizza et al., 2013) and restless legs syndrome (RLS) is frequent in NT1 (Plazzi et al., 2010) with a probable different pathophysiology than primary RLS (Barateau et al., 2020a). REM sleep abnormalities, vivid dreams, nightmares, REM sleep without atonia (RSWA) and REM sleep behaviour disorder (RBD) are observed in 25%–70%, and non-REM sleep parasomnias occasionally reported (Dauvilliers et al., 2007c, 2013a; Knudsen et al., 2010). NT1 is the most frequent cause of RBD in young patients (Bonakis et al., 2009), being a common sleep comorbidity also in children (Antelmi et al., 2017). Patients with NT1 present indeed dissociated sleep features, frequent shift from REM to non-REM sleep, and mixed sleep stages with RSWA (Dauvilliers et al., 2007c; Schenck & Mahowald, 1992), a persistence of muscle tone, excessive twitching during REM sleep (Antelmi et al., 2017). RBD is reported in NT1 in up to 60% of patients, while its prevalence in NT2 remains unclear (Dauvilliers et al., 2007c, 2013a). In contrast to idiopathic RBD (iRBD), there is no gender predominance, movements are elementary rather than complex, behavioural manifestations are less violent, and age at onset is earlier in NT1. Higher percentages of RSWA, phasic electromyographic activities and REM density were reported in narcoleptic patients compared with controls, even in the absence of any REM sleep behavioural manifestation. Of interest, cardiac sympathetic activity differentiates iRBD and NT1 with RBD (Barateau et al., 2018a). Other REM-related parasomnias are reported by narcoleptic patients, such as vivid and unpleasant dreams, and sometimes recurrent nightmares.

There is a higher frequency of cardiovascular diseases in narcolepsy (Jennum et al., 2021; Ohayon, 2013), and patients report clinical autonomic impairment (Barateau et al., 2019a). Hypertension and lack of nocturnal blood pressure dipping are prevalent, between 30% and 50% of patients, and also observed in animal models, and need to be carefully monitored in the long term (Bosco et al., 2018; Jennum et al., 2021). Cardiac sympathetic innervation is normal in NT1, but patients with cardiovascular comorbidities and REM sleep motor deregulation are potentially at higher risk (Barateau et al., 2019b). Obesity and overweight are frequent in narcolepsy: up to one-third of patients are obese (Kok et al., 2003; Kotagal et al., 2004), and half of children, especially at the onset of the disease. The cause of this tendency to gain weight is not known, but might be linked to Hcrt deficiency. Recently, we showed that a distinct metabolic profile in the sera can differentiate controls and patients with NT1, as a function of body mass index (BMI), and proposed some metabolic diagnostic biomarkers for NT1, namely glutamate, sarcosine, serotonin, tryptophan, nonaylcarnitine and some phosphatidylcholines (Dauvilliers et al., 2022). As a result of this overweight, obstructive sleep apnea is often reported in narcolepsy, especially in adults, with a prevalence ranging from 10% to 20% (Sansa et al., 2010). Narcoleptic patients also present other cardiovascular risk factors such as diabetes type 2 and metabolic syndrome (Jennum et al., 2013; Poli et al., 2009). A recent study demonstrated that mice subjected to sleep fragmentation develop larger atherosclerotic lesions and produce less Hcrt, in favour of a neuro-immune axis that links sleep to haematopoiesis and atherosclerosis (McAlpine et al., 2019). Whether this observation is transposable in humans still needs to be tested.

Psychiatric comorbidities are frequent in NT1, including mood, anxiety, ADHD, eating disorders, suicidal thoughts and rarely psychosis (Barateau et al., 2020c; Dauvilliers et al., 2009). The high frequency of depressive symptoms supports the hypothesis of an endogenous depression, and narcolepsy shares with major depression a reduced nighttime REM sleep latency, and an increased REM sleep pressure and sleep fragmentation (Barateau et al., 2017c; Dauvilliers et al., 2013b).

The phenotype of narcolepsy can vary from one patient to another, not only for the main features of the disease (frequency of cataplexy, severity of EDS or disturbed nocturnal sleep), but also regarding comorbidities (obesity, RLS, RBD, apnea, depressive symptoms). This complex phenotype is well described in narcolepsy but may vary over time for a patient, in NT1 but also in NT2, although less robust data are available in the latter. This heterogeneity and the determinants of all these characteristics need to be further studied as a function of the narcolepsy spectrum, both in NT1 and in NT2.

2.6 | Evolution of the disease

The natural history of the loss of Hcrt neurons and CSF Hcrt-1 levels in NT1 remains largely unknown, and the gradient and slope of the

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destruction of Hcrt neurons could vary among narcoleptic patients. Indeed, some patients develop a severe narcolepsy with cataplexy phenotype within a few days or weeks, while others develop a progressive disease with first EDS and then cataplexy months or years later (Dauvilliers et al., 2001). In addition, a progressive decrease in CSF Hcrt-1 levels over time was reported in some patients with NT1, who underwent a second lumbar puncture along disease severity worsening (Lopez et al., 2017a; Pizza et al., 2014), as well as in patients with intermediate CSF Hcrt who presented clear narcolepsy symptoms (Postiglione et al., 2022). In NT1, the clinical course is often stable but difficult to predict, with an important variability among patients. EDS and cataplexy frequency can improve with age, whereas nocturnal sleep usually worsens. On the Multiple Sleep Latency Test (MSLT), patients have less sleep-onset REM periods (SOREMP) and a longer sleep latency when getting older. In contrast, the clinical course of NT2 is highly variable: some patients improve spontaneously, others show complete remission with time (Trotti et al., 2013). Rarely, NT2 patients may also later develop cataplexy, and are then reconsidered as NT1 patients (Andlauer et al., 2012). Also, a phenotypic overlap exists between NT2 and idiopathic hypersomnia, another rare central hypersomnolence disorder, with difficulties in clearly separating these entities with current criteria (AASM, 2014; Lammers et al., 2020). Finally, due to frequent fluctuations of NT2 (but also idiopathic hypersomnia) severity over time and spontaneous remissions, the persistence of the disorder should be regularly reevaluated with repeated comprehensive investigations after withdrawal from the stimulant treatment (Lammers et al., 2020).

3 | DIAGNOSIS

Narcolepsy type 1 was called "narcolepsy with cataplexy" before 2014 (AASM, 2005), but was renamed NT1 in the third and last international classification of sleep disorders (AASM, 2014). The validity of the diagnostic criteria improved, and the new criteria included the underlying pathophysiology and the fact that patients may present without cataplexy (or without typical cataplexy). NT1 diagnosis confirmation requires a nocturnal PSG followed by MSLT, or CSF Hcrt-1 measurement, according to ICSD-3 (AASM, 2014). NT1 is defined as the presence of sleepiness for more than 3 months (even if this timing is now debated), associated with either: (1) the presence of clear cataplexy, a mean sleep latency ≤8 min on the MSLT, and at least two SOREMPs during the MSLT (or a SOREMP at night and at least one on MSLT); or (2) CSF Hcrt-1 deficiency (Hcrt-1 level below 110 pg ml^{-1}). A low level of Hcrt-1 in the CSF is very sensitive and specific for the diagnosis of NT1. Hcrt-1 levels have to be determined in duplicate by direct I^{125} radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA, USA), then all values back-referenced to the Stanford reference samples (Stanford University Center for Narcolepsy, Palo Alto, CA, USA). CSF Hcrt-1 levels ≤ 110 pg ml^{-1} are considered low, between 110 and 200 pg ml^{-1} intermediate, and > 200 pg ml^{-1} normal (Dauvilliers et al., 2003a; Mignot et al., 2002). The measurement of Hcrt-1 based on a multiple reaction monitoring approach may provide a useful alternative to radioimmunoassay to quantify CSF Hcrt-1 (Hirtz et al., 2016).

All patients with low CSF Hcrt-1 levels are considered as NT1 patients, even if they report no cataplexy (in about 10–20% of cases), and all patients with normal CSF Hcrt-1 levels (or without cataplexy when the lumbar puncture is not performed) as NT2 patients (Baumann et al., 2014). Of interest, a SOREMP on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT, based on findings obtained in a large cohort of narcoleptic patients (Andlauer et al., 2013). We recently established MSLT cutoffs in children, showing that at least 2 SOREMPs or (instead of "and") a mean sleep latency ≤ 8.2 min on MSLT are valid and reliable markers for NT1 diagnosis, contrasting with criteria for adults (Pizza et al., 2019), but age in this group of children and adolescents surprisingly did not influence MSLT results.

In contrast to NT1, NT2 is still poorly understood, and less well-defined, probably heterogeneous, diagnosed on clinical and neurophysiological criteria only, with unspecific and unstable biomarkers, and high phenotype variability (Evangelista et al., 2018; Lopez et al., 2017b). It is defined by the presence of EDS without cataplexy for longer than 3 months, with mean sleep latency on the MSLT ≤ 8 min, at least 2 SOREMPs on the MSLT (or PSG), and Hcrt-1 level higher than 110 pg ml^{-1}, if measured. EDS has to be non-comorbid, and not better explained by another cause: for instance, sleep deprivation, obstructive sleep apnea syndrome, circadian rhythm disorders, or the effect of a medication or substance abuse. False-positive diagnosis may thus occur, especially with chronic insufficient sleep syndrome that may cause early REM sleep intrusions into sleep (Goldbart et al., 2014). If cataplexy appears over time in a NT2 patient (sometimes many years later), or if a Hcrt-1 level is below 110 pg ml^{-1} (even without cataplexy), the condition is reclassified as NT1. Altogether, the diagnosis of NT2 is still a challenge, and it remains unclear whether NT2 is a distinct entity, and distinct to idiopathic hypersomnia, as detailed above. A recent work based on a supervised machine learning approach has highlighted the usefulness of combining various sources of assessment, especially the presence and the characteristics of cataplexy to distinguish NT1 from NT2 diagnoses (Zhang et al., 2018). Recently, sleep experts discussed and proposed new criteria, to better categorize these patients in future classifications (Fronczek et al., 2020; Lammers et al., 2020). Also, patients with intermediate CSF Hcrt-1 levels (between 110 and 200 pg ml^{-1}) may also be on the narcolepsy spectrum with an "incomplete form of NT1", an extremely rare and heterogeneous condition (Postiglione et al., 2022). At last, hereditary and secondary forms of narcolepsy, and narcolepsy-like phenotypes also exist, but not all of them display Hcrt-1 deficiency in the CSF (Moghadam et al., 2014).

4 | EPIDEMIOLOGY

Narcolepsy type 1 is an orphan disease, affecting about 20–50/100,000 Caucasians worldwide (Ohayon et al., 2002). However, most epidemiological studies are questionnaire- or interview-based,

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and only a few included objective tests such as MSLT (Silber et al., 2002), none have included CSF Hcrt-1 measurements. A study suggested that the incidence rate per 100,000 persons per year was 1.37 (1.72 for men and 1.05 for women), with the highest incidence in the second decade. The prevalence was 56.3 per 100,000 persons. Approximately 36% of prevalence cases did not have cataplexy (Silber et al., 2002). The median delay from the onset of symptoms to diagnosis reaches more than 10 years (Luca et al., 2013; Thorpy and Krieger, 2014), and the age of onset of NT1 varies widely, but symptoms usually appear within the first two decades of life (Dauvilliers et al., 2001), with a bimodal distribution (15 years old and 35 years old). A link has been shown between the development of NT1, H1N1 influenza vaccination and H1N1 infection (Partinen et al., 2014). As the diagnosis of NT2 is not based on very robust specific criteria, there are no valid epidemiological data. This disorder might be under-, but also over-diagnosed, as other common conditions such as chronic insufficiency sleep syndrome and shift workers can mimic NT2 clinical and electrophysiological hallmarks.

5 | PATHOPHYSIOLOGY

A major breakthrough occurred in 2000, with the discovery of the loss of a small population of neurons that synthesizes Hcrt responsible for NT1 pathophysiology (Peyron et al., 2000; Thannickal, 2000). Post-mortem studies identified a selective loss of Hcrt cells in the lateral hypothalamus in the brain of narcoleptic patients with cataplexy. Hcrt-1 and -2 (also known as orexin-A and -B) are endogenous arousal-promoting neuropeptides (de Lecea et al., 1998; Sakurai et al., 1998), and Hcrt neurons represent a restricted group of 70–80,000 cells of the lateral hypothalamus. They project widely to multiple neuronal systems, and play a major role in several physiological functions such as the regulation of the sleep–wake cycle, neuroendocrine and autonomic functions, reward system, emotional behaviours, body temperature and metabolism (Peyron et al., 1998). Also, a large increased number of histaminergic neurons was unexpectedly found in patients with NT1 (Valko et al., 2013), with controversial findings reported in mouse models of narcolepsy (Shan et al., 2015). We recently showed that the expression of histamine but also noradrenaline are not modulated by Hcrt level whether the lack of Hcrt is constitutive or induced at adult age, showing thus no compensation. We also found no recruitment of histamine by local neuroinflammation (Melzi et al., 2022). Further studies will be needed to further define the role of histamine in the pathophysiology of NT1. Very recently, a selective decrease in corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus was further discovered in NT1 post-mortem, while CRH neurons in the locus coeruleus and thalamus, and other paraventricular nucleus neuronal populations were spared (Shan et al., 2022).

The severity of EDS and cataplexy may correlate with the extent of Hcrt neurons loss and with the decrease in CSF levels of Hcrt-1 (Gerashchenko et al., 2003; Thannickal et al., 2009), and it has been hypothesized that in some patients, NT2 may be caused by partial loss of Hcrt neurons, with a continuum in pathophysiology with NT1. If most patients with narcolepsy without cataplexy have normal CSF Hcrt-1 levels (Dauvilliers et al., 2003a), a loss of Hcrt neurons below 50% of normal levels has been reported in a few patients with NT2 and may thus correspond to rodent models (Black et al., 2018; Thannickal et al., 2009). Of interest, animal models of partial Hcrt loss exhibit EDS but not cataplexy (Gerashchenko et al., 2001).

Anatomical, electrophysiological and behavioural studies showed that the Hcrt system promotes and stabilizes wakefulness (Kiyashchenko et al., 2002; Lee et al., 2005; Mileykovskiy et al., 2005), and the loss of Hcrt neurons impairs survival of long wake bouts resulting in poor maintenance of wakefulness. Hcrt release is highest during wakefulness, and lowest during sleep. Hcrt neurons project widely to various brain regions: olfactory bulb, cerebral cortex, thalamus, hypothalamus, locus coeruleus, dorsal raphe, tuberomammillary nucleus, latero-dorsal tegmentum/pedunculopontine nucleus and the basal forebrain. They stimulate neurons of those regions that produce norepinephrine, dopamine, serotonin and histamine, with long-lasting effects allowing the maintenance of wakefulness through the day. Hcrt cell loss probably destabilizes those circuits promoting arousal, and produces sleepiness and deregulation of REM sleep. If Hcrt deficiency is believed to be the main cause of EDS, several down- and upstream projecting aminergic neurotransmitters could also have a role. In a recent study, we found no striking differences among CSF monoamines, their metabolites and trace amine levels in NT1/NT2, idiopathic hypersomnia, and patients without objective sleepiness (Barateau et al., 2021a).

The Hcrt increases activity in brain regions that suppress REM sleep, thus reduced Hcrt signalling may trigger components of REM sleep leading to sleep paralysis, hypnagogic hallucinations and cataplexy. Cataplexy is triggered by strong positive emotions that can be relayed by the medial prefrontal cortex that activates the Hcrt neurons and neurons in the central nucleus of the amygdala, which for the former activate the ventral lateral periaqueductal grey and the lateral pontine tegmentum for Hcrt neurons but instead inhibit them via the amygdala (Meletti et al., 2015; Vaudano et al., 2019). Under normal conditions, the latter regions (i.e. ventral lateral periaqueductal grey and the lateral pontine tegmentum) inhibit the sublatero-dorsal nucleus, a region that during REM sleep causes muscle atonia by activating γ-aminobutyric acid (GABA)ergic premotor neurons that inhibit motoneurons (Mahoney et al., 2019). In patients with NT1, the absence of Hcrt leads to the inhibition of regions that suppress REM sleep, thus allowing the activation of descending pathways inhibiting motoneurons, leading to cataplexy.

The identification of the cause of narcolepsy, and the determination of the mechanisms underlying the symptoms have been possible thanks to several animal models. Across species (humans, mice, dogs), a defect in Hcrt signalling indeed leads to a narcoleptic phenotype with sleepiness, cataplexy, SOREM periods and sleep fragmentation (Chemelli et al., 1999), and substantial similarities in basic biology of the Hcrt system. The exponential progress of knowledge in this field has been fueled by the translational research from animals to humans. The first animal model was narcoleptic dogs, with a mutation in the

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Hcrt-2 receptor gene (Lin et al., 1999), subsequently leading to the discovery that the loss of Hcrt neurons causes human narcolepsy (Peyron et al., 2000; Thannickal, 2000). Mouse models are mainly used today, by a genetic disruption of the hypocretinergic neurotransmission or the destruction of Hcrt neurons. They allow the identification of the normal physiological role of the Hcrt system: sleep/wake regulation, but also metabolism, feeding, mood, motivation and reward. More recently, new animal models were created to study the mechanisms and processes to explain the loss of Hcrt neurons. In transgenic mice expressing influenza virus protein haemagglutinin in the Hcrt cells, Hcrt neurons were destroyed after injection of activated antigen-specific cytotoxic $CD8^+$ T-cells, leading to sleep attacks, disturbed sleep and cataplexy (Bernard-Valnet et al., 2016). This model demonstrates the potential role of cytotoxic CD8+ T-cells as final effectors of the immunopathological process in narcolepsy. In another model, mice lacking B- and T-cells were infected with a H1N1 influenza A virus strain, and the infection targeted several brain structures of the sleep–wake-regulating neuronal network, destroying Hcrt neurons, and leading to sleep–wake changes (Tesoriero et al., 2016). In a third recent model, Hcrt cells were conditionally ablated, with a system that controls diphtheria toxin-A accumulation in Hcrt neurons, allowing a temporal neuronal degeneration. Normal sleep architecture was disrupted after the loss of 80% of Hcrt neurons, whereas cataplexy only developed once 95% of cells were lost (Tabuchi et al., 2014).

The exact underlying process leading to the destruction of Hcrt neurons remains unclear, but it is widely accepted by the scientific community that NT1 is probably an autoimmune or dysimmune disease (Kornum et al., 2017). A growing body of evidence supports this hypothesis, and major arguments are summarized in several recent reviews (Barateau et al., 2017a). Many epidemiological, biological and clinical findings favour this hypothesis: rare family cases and frequent discordance in monozygotic twins, young and bimodal age at onset, association with the 2009 H1N1 influenza pandemic and its vaccine *Pandemrix*, and possibly with streptococcal infections in some cases. We also recently provided evidence of gut microbial community structure alterations in NT1 in a preliminary study (Lecomte et al., 2020). Genetic background is of key importance in NT1, as more than 98% of patients with NT1 carry the Class II Human Leukocyte Antigen (HLA) DQB1*06:02 allele, versus 25% of the general population, being the strongest association ever reported in a disease with an HLA gene allele. More recently, the role of HLA Class I and other immune gene variants was highlighted, as purinergic receptor *P2RY11*, and T-cell receptor alpha locus *TRA*. In a seminal paper, a highly sensitive method was used to detect populations of rare T-cells, with the findings of polyclonal autoreactive CD4+ T-cells recognizing different epitopes of the prepro-Hcrt peptide in NT1, also in a few patients with NT2, unlike healthy controls (Latorre et al., 2018). Using a different method, another seminal paper suggested the possibility that an autoimmune process targeting Hcrt neurons might be triggered by molecular mimicry with the influenza virus. They showed a higher reactivity to several epitopes derived from influenza pandemic H1N1 (haemagglutinin and nucleoproteins) and the C-amidated (but not native) form of Hcrt in NT1 (Luo et al., 2018). In contrast, no specific pathogenic antibodies against Hcrt neurons have been discovered so far in NT1. This could be due either to the immune activation of T-cells specifically, or to a very small number of antibodies, with a damaged cerebral area very restricted, and potentially transient. Indeed, another explanation could be the time course of the disease: when the patient is symptomatic, Hcrt neurons could be already irreversibly destroyed. If the immune-based origin of NT1 is almost ascertained, its pathophysiology is probably unique, and even still controversial. There is no striking association with other immune-based disorders in NT1, unlike many autoimmune diseases (Barateau et al., 2017b). No clear signs of inflammation in the hypothalamic area were found in the narcoleptic brains (Peyron et al., 2000), even though a study found a higher number of astrocytes in the hypothalamus of NT1 patients compared with controls (Thannickal, 2000). To summarize, the current hypothesis is that environmental triggers such as viral or bacterial infections, in subjects with a genetic predisposition may lead to immune activation of CD4+ and CD8+ T-cells, with a proinflammatory signature of T-cells dominated by elevated levels of B-cell-supporting cytokines, resulting in Hcrt cell destruction. Investigation on the autoimmune aetiology of NT1 is a very dynamic field of research, with the exponential development of advanced new techniques, and many recent exciting findings published in these last years (Beltrán et al., 2019; Hartmann et al., 2016; Latorre et al., 2018; Luo et al., 2018; Pedersen et al., 2019). Conversely, pathophysiological mechanisms underlying NT2 remain largely unknown, certainly heterogeneous and polymorphic.

6 | MANAGEMENT

The current treatment of narcolepsy is only symptomatic, despite recent major advances in understanding its mechanisms (Barateau & Dauvilliers, 2021, 2019). Management strategies are codified in NT1, with a lifelong treatment required. In contrast, rare pharmacological studies focused on NT2 patients, and physicians should always keep in mind that a spontaneous improvement or disappearance of the symptoms is possible. Non-pharmacological strategies must always be considered, including behavioural and psychosocial treatment strategies (Bassetti et al., 2021). Psychoeducation of the patient, maintaining good sleep hygiene, with regular night-time sleep schedule, short scheduled naps across the day, physical activity and weight control should be systematically added to the pharmacological interventions. Joining a patient organization is a source of exchange and support, and promotes better disease acceptance and treatment adherence.

Among medication options, a single drug can target several symptoms, or multiple medications each treat a specific symptom (Barateau et al., 2016). Considering the unique pathophysiology of NT1, Hcrt replacement therapy is the most interesting alternative in the future, and Hcrt receptor-2 agonists are very promising candidates to treat narcolepsy. A third possibility would be to prevent the destruction of Hcrt neurons by immunomodulatory agents, at the onset of NT1, to

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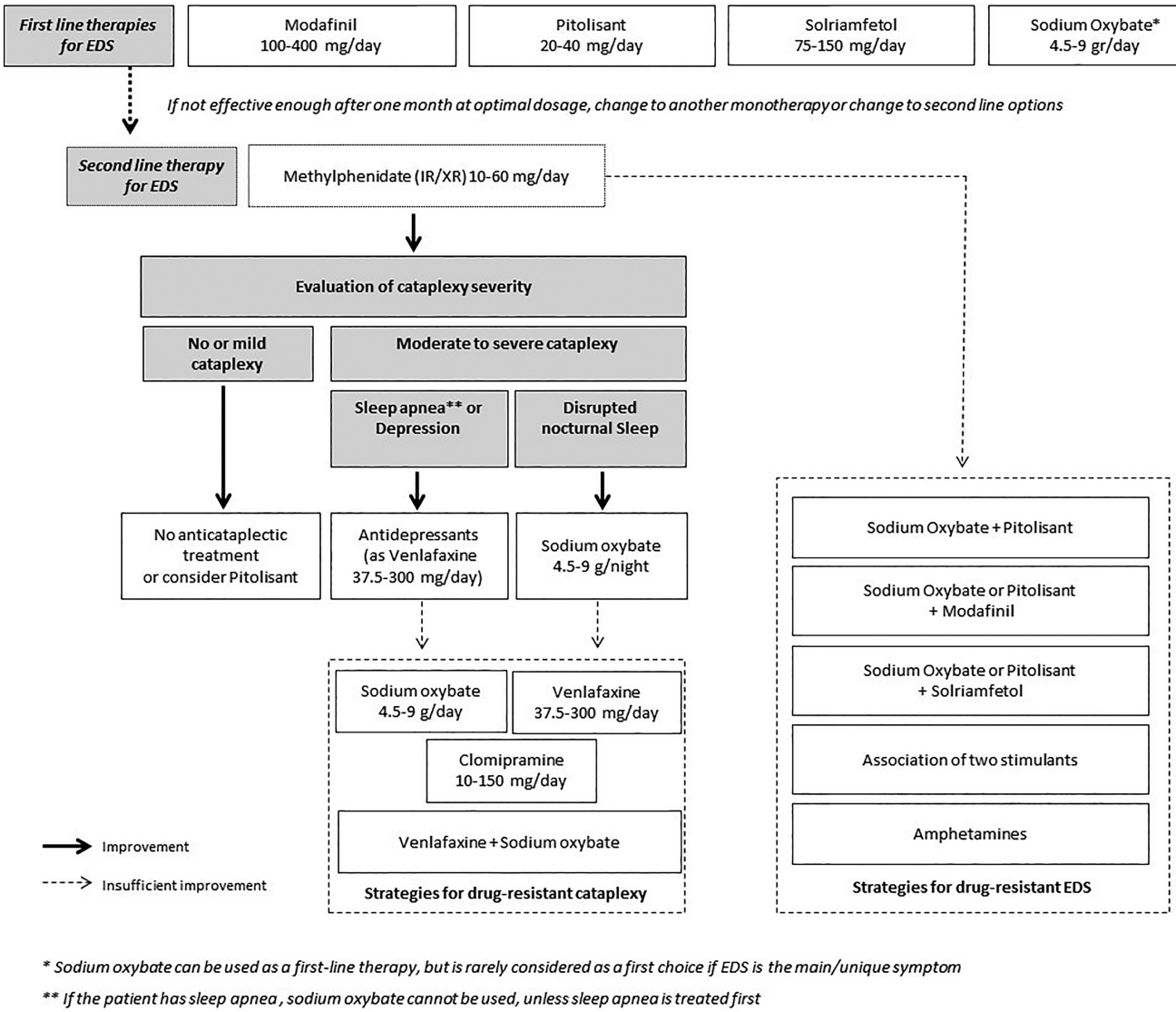

FIGURE 1 Decision tree for managing sleepiness and cataplexy in narcolepsy type 1 (NT1). Adapted from Barateau and Dauvilliers (2021). DNS, disrupted nocturnal sleep; EDS, excessive daytime sleepiness; IR, immediate release; XR, extended release

modify its clinical course. However, attempts to use such therapies on uncontrolled case studies, and with small numbers of patients, have shown often disappointing results, as we summarized in recent review papers (Barateau et al., 2017a; Giannoccaro et al., 2020). However, some patients may have an "inflammatory" process still ongoing at time of evaluation, and they may respond better to immune therapies in future clinical trials.

6.1 | Current recommended medications

Symptomatic treatments are the main recommended strategy, with a good evidence level (level A): psychostimulants to manage EDS, antidepressant agents for cataplexy, and sodium oxybate for both symptoms (Barateau et al., 2016). This last drug can also improve DNS (Roth et al., 2017). The European Medicine Agency and the US Food and Drug Administration approved most of these drugs (i.e. psychostimulants and sodium oxybate), but others are used off-label, on the basis of their recognized utility by expert consensus, for example antidepressant agents for cataplexy. Recent reviews provided the details of recommended management strategies in narcolepsy: European Sleep Research Society and American Academy of Sleep Medicine guidelines (Bassetti et al., 2021; Maski et al., 2021). A decision tree for adapting the therapy in NT1 is shown in Figure 1. First-line medications should be wake-promoting agents/psychostimulants such as modafinil, armodafinil (not available in Europe), pitolisant, solriamfetol or sodium oxybate. Modafinil/armodafinil increases the extracellular concentration of dopamine by blocking its transporter. Pitolisant is a recent wake-promoting agent that activates histamine neurons, acting as a selective histamine H3 receptor inverse agonist (Szakacs et al., 2017). Solriamfetol is a psychostimulant that is a phenylalanine derivative with dopaminergic and noradrenergic activity

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(Thorpy et al., 2019). Sodium oxybate is different, it stimulates GABA-B receptors, with a modulating effect on GABAergic, noradrenergic and dopaminergic neurons, as well as on thalamo-cortical neurons. This drug is taken at night and promotes slow-wave sleep. It has an effect on nocturnal sleep, cataplexy and EDS, with a maximum effect on these two last symptoms after a few weeks. Second-line medications are methylphenidate, with a low level of evidence, and amphetamines are third-line therapy for EDS, because of their potential risk of abuse, psychiatric and cardiovascular adverse effects. In theory, tolerance may develop for all stimulants, but this condition is rare in patients with NT1, and the absence of Hcrt might explain the low rate of addiction (Barateau et al., 2015). To manage cataplexy, sodium oxybate is the first-line strategy; however, pitolisant was also reported to be effective in cataplexy. Antidepressants (selective serotonin and dual serotonin and noradrenaline reuptake inhibitors) are also widely used, very efficient and with few side-effects, but based on expert consensus only because randomized controlled trials are lacking. At last, different compositions of sodium oxybate, for example, low-salt, and long acting formulations have been recently developed (Bogan et al., 2020; Kushida et al., 2021).

Treatment strategies for children with narcolepsy are quite similar to those proposed for adults (Bassetti et al., 2021); however, to date only sodium oxybate is approved in children with narcolepsy (Plazzi et al., 2018). A particular attention is needed when evaluating safety (mood, cardiovascular and metabolic problems) and the risk-to-benefit ratio of any treatment, especially in children. Stimulants such as methylphenidate are approved for children with ADHD and also with narcolepsy in some countries. Modafinil is not approved due to side-effects with rare allergic reactions and rashes. Results from well-designed trials using pitolisant and solriamfetol are currently lacking. In addition to sodium oxybate, pharmacological treatment of cataplexy may include off-label use of selective serotonin reuptake inhibitors and selective serotonin norepinephrine reuptake inhibitors (Bassetti et al., 2021). Objective and self-reported measures of symptoms are required to monitor the treatment efficacy in clinical settings and in research studies, such as the Narcolepsy Severity Scale (NSS) developed for adults (Dauvilliers et al., 2017), and its version for school-aged children and adolescents, the NSS-P (Barateau et al., 2021b), and finally the maintenance of wakefulness test for driving safety and licence in several countries (Krahn et al., 2021). We also recommend carefully monitoring safety issues, especially depressive symptoms, BMI and cardiovascular parameters such as drug-induced blood pressure changes. The choice of appropriate drugs should be based on the presence and severity of different symptoms, but also the patient's characteristics and comorbid conditions (obesity, apneas, metabolic, cardiovascular, psychiatric comorbidities); Table 1).

TABLE 1 Interactions between drugs for narcolepsy and comorbidities (expert opinion; adapted from Barateau et al., 2016)

	May improve	May worsen
Obesity, diabetes	Sodium oxybate	Tricyclic agents, other antidepressants
Cardiovascular diseases	–	Stimulants (except pitolisant)
Mood disorders	Antidepressants (for depressive symptoms, with moderate response)[a]	Sodium oxybate (for depressive symptoms) Stimulants (for manic/mixed episode)
Psychotic disorders	Aripiprazole	Stimulants (except pitolisant)
ADHD	Methylphenidate	–
OSAS	–	Sodium oxybate
RLS	–	Sodium oxybate Antidepressants
SW/ST, enuresis	–	Sodium oxybate
REM sleep behaviour disorder	Sodium oxybate	Antidepressants

Abbreviations: ADHD, attention deficit hyperactivity disorder; OSAS, obstructive sleep apnea syndrome; REM, rapid eye movement; RLS, restless legs syndrome; SW, sleepwalking; ST, sleep terrors.
[a]Doses used to manage cataplexy are usually lower than doses used for depression.

7 | CONCLUSION

The integration of data from multiple approaches in animal models and humans increased our understanding of narcolepsy, but patients need to be screened more effectively and earlier to optimize diagnosis and management, not only at a pharmacological level but also with a global approach taking into account patients' educational, social and professional needs. Further effort should be made in future research to investigate larger groups of patients, with similar characteristics at baseline, which is feasible by the use of collaborative networks and registries, such as the European Narcolepsy Network (EU-NN). This is mandatory to understand and explore the determinants of the characteristics and comorbidities in narcolepsy, with the perspective to propose personalized medicine to patients. Identifying reference centres at National and European levels will help to guarantee to patients a high standard of cure, and to explore the usefulness of alternative screening and follow-up methods by telemedicine (Ingravallo et al., 2020) and wearable monitoring systems (Filardi et al., 2018a,b, 2016) for screening and follow-up. Contrasting with the important knowledge about the pathophysiology of NT1, its features, comorbidities and consequences, there is a dearth of knowledge about other central disorders of hypersomnolence such as NT2 and idiopathic hypersomnia. Other studies are needed to characterize these disorders, and to discover reliable biomarkers (genetic, biology, imaging, neurophysiology). Hcrt neuropeptides and narcolepsy are very active areas for research, and the upcoming arrival of non-peptide Hcrt receptor-2 agonists as new therapies will open new exciting perspectives for researchers and bring hope to patients with narcolepsy, but also maybe other disorders beyond NT1.

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AUTHOR CONTRIBUTIONS

Lucie Barateau wrote the first draft; Lucie Barateau and Yves Dauvilliers drafted the manuscript, that was reviewed, modified and approved by Fabio Pizza and Giuseppe Plazzi.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this article. Y. D. received funds for seminars, board engagements and travel to conferences by UCB Pharma, Jazz, Orexia, Idorsia, Takeda, Avadel and Bioprojet. L. B. received funds for travelling to conferences by UCB Pharma and Bioprojet speaking honoraria from UCB Pharma, JAZZ and Bioprojet; board engagements from Jazz, Bioprojet and Takeda. F. P. received funds for travelling to conferences (Bioprojet), for speaking at symposia (Jazz), and for participating to advisory board (Takeda). G. P. received funds for board engagements from Jazz, Bioprojet and Takeda.

DATA AVAILABILITY STATEMENT

NA

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