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Narcolepsies, update in 2023

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ABSTRACT

Narcolepsy type 1 (NT1) and type 2 (NT2), also known as narcolepsy with and without cataplexy, are sleep disorders that benefited from major scientific advances over the last two decades. NT1 is caused by the loss of hypothalamic neurons producing orexin/hypocretin, a neurotransmitter regulating sleep and wake, which can be measured in the cerebrospinal fluid (CSF). A low CSF level of hypocretin-1/orexin-A is a highly specific and sensitive biomarker, sufficient to diagnose NT1. Orexin-deficiency is responsible for the main NT1 symptoms: sleepiness, cataplexy, disrupted nocturnal sleep, sleep-related hallucinations, and sleep paralysis. In the absence of a lumbar puncture, the diagnosis is based on neurophysiological tests (nocturnal and diurnal) and the presence of the pathognomonic symptom cataplexy. In the revised version of the *International Classification of sleep Disorders, 3rd edition* (ICSD-3-TR), a sleep onset rapid eye movement sleep (REM) period (SOREMP) (i.e. rapid occurrence of REM sleep) during the previous polysomnography may replace the diurnal multiple sleep latency test, when clear-cut cataplexy is present. A nocturnal SOREMP is very specific but not sensitive enough, and the diagnosis of cataplexy is usually based on clinical interview. It is thus of crucial importance to define typical versus atypical cataplectic attacks, and a list of clinical features and related degrees of certainty is proposed in this paper (expert opinion). The time frame of at least three months of evolution of sleepiness to diagnose NT1 was removed in the ICSD-3-TR, when clear-cut cataplexy or orexin-deficiency are established. However, it was kept for NT2 diagnosis, a less well-characterized disorder with unknown clinical course and absence of biolo biomarkers; sleep deprivation, shift

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working and substances intake being major differential diagnoses. Treatment of narcolepsy is nowadays only symptomatic, but the upcoming arrival of non-peptide orexin receptor-2 agonists should be a revolution in the management of these rare sleep diseases.

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1. Abbreviations

CSF	cerebrospinal fluid
DNS	disrupted nocturnal sleep
EDS	excessive daytime sleepiness
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICSD	International classification of sleep disorders
ICSD-3	International classification of sleep disorders third edition
ICSD-3-TR	International classification of sleep disorders third edition, text revision
MSLT	multiple sleep latency test
NT1	narcolepsy type 1
NT2	narcolepsy type 2
PSG	polysomnography
REM sleep	rapid eye movement sleep
SNRI	serotonin and norepinephrine reuptake inhibitors
SOREMP	sleep onset REM period
SSRI	selective serotonin-reuptake inhibitors

2. Introduction

Central disorders of hypersomnolence are characterized by a persistent complaint of excessive daytime sleepiness (EDS), a frequent symptom in the general population and in many other sleep disorders. Nevertheless, some red flags should prompt physicians to consider the possibility of a rare condition, narcolepsy. Following warning signs when evaluating EDS should raise suspicion of narcolepsy: a child or a young adult exhibiting symptoms such as rapid weight gain over a few months to a year, early puberty, short and refreshing naps, dreamlike activity during naps, sleep paralysis, sleep-related hallucinations, and cataplexy. The median delay from the onset of symptoms to diagnosis is still too long and reaches more than 10 years [1–3], likely due to a lack of knowledge about the condition. Providing the medical community with information on the diagnosis of narcolepsy is crucial, given the major impact of this condition on patient functioning, accidentology, and quality of life. In addition, advances in our understanding of the pathophysiology of this rare but well-characterized disease offer a more general insight into the mechanisms involved in the regulation of wake and sleep.

In this review, we provide a comprehensive examination of the clinical manifestations, laboratory assessments, pathophysiological aspects, management approaches of two central hypersomnolence disorders, narcolepsy type 1 (NT1), formerly known as narcolepsy with cataplexy, and type 2 (NT2), without cataplexy. Following the recent publication of the revised *International Classification of Sleep Disorders, 3rd Edition* (ICSD-3-TR) [4], we also highlight and comment the few novelties regarding narcolepsy.

3. Prevalence

NT1 is a rare neurological disorder, affecting approximately 0.026% of the general population, and both sexes are affected [5]. Narcolepsy typically emerges during adolescence or young adulthood: the age of onset of NT1 varies widely, but symptoms usually appear within the first two decades of life, with a bimodal distribution at 15 and at 35 years old [6]. Symptoms remain present throughout the patient's life. While symptoms may intensify after their initial appearance, as well as appear abruptly in children with subsequent amelioration, they can also show improvement across the disease course, except for the disrupted nocturnal sleep that may worsen with age.

4. Symptoms

The "narcoleptic pentad" comprises five primary symptoms that are typically observed in NT1: EDS, cataplexy, disturbed nocturnal sleep (DNS), sleep paralysis and sleep-related hallucinations. Other symptoms are commonly reported by patients: fatigue, brain fog, attention problems (difficulties with sustaining a purposeful focus on stimuli), cognitive disorders, particularly memory complaints, and emotional difficulties, including irritability, impulsivity, and distractibility [7]. These symptoms are not specific to narcolepsy and may be related to sleepiness, although further studies are needed for their characterization in narcoleptic populations, and across the life span [8].

4.1. *Sleepiness*

EDS most typically emerges as the initial symptom, primarily affecting young adults and presenting as the most severe manifestation [9]. Daytime sleep episodes have distinctive characteristics: they are often difficult to resist, of short duration, with an occurrence also from the early morning, and are frequently accompanied by dreaming. They leave the patient feeling "refreshed", and are followed by a return to a normal (at least temporarily) level of alertness [5]. When sleepiness is severe (and especially if the patient fights against sleepiness), individuals may experience unconscious microsleep episodes or lapses, as well as a semi-automatic continuation of their actions, leading to inappropriate words during a conversation or automatic writing of unrelated content, called "automatic behaviors".

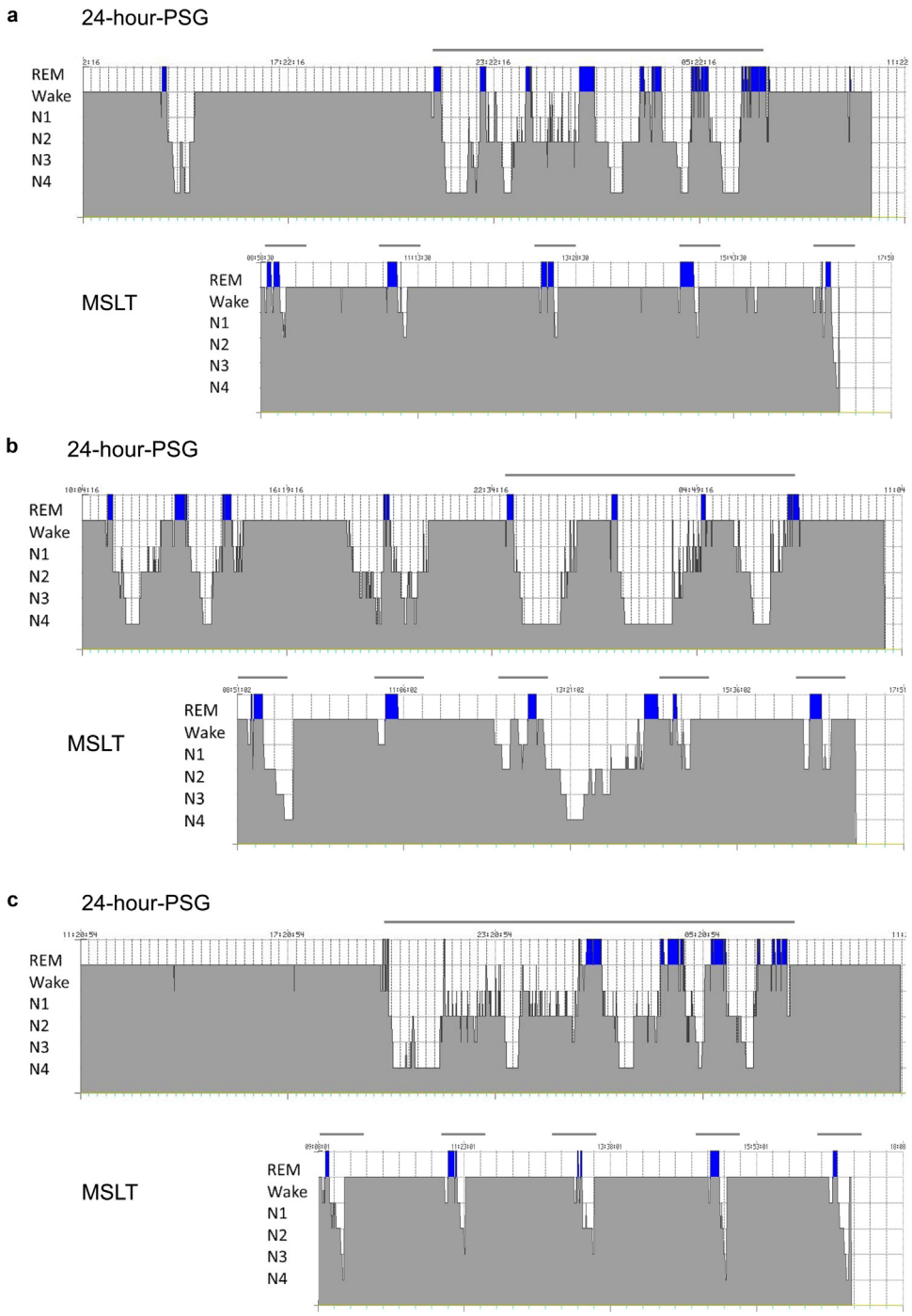

Fig. 1 – Three examples of children with narcolepsy type 1 with different excessive daytime sleepiness phenotypes on MSLT and 24-hour-polysomnography. N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3 (slow wave sleep); N4: stage 4 (former classification, deeper slow wave sleep); MSLT: multiple sleep latency test; PSG: polysomnography; REM: rapid eye movement.

4.2. *Cataplexy*

Cataplexy is the pathognomonic symptom of NT1, but the phenotype differs widely between patients. As patients are rarely examined during an episode of cataplexy, its presence needs to be first established based on clinical history, second, if possible, by video recordings with smartphone by family members , and third by video recordings in sleep laboratories [10]. Albeit it is difficult to see a cataplectic attack at clinical examination, it may be easily evoked by applying a semi standardized approach or it can be documented at home by video recordings [11].

A cataplexy is a sudden loss of voluntary muscle control without any impairment of consciousness [12]. It is unpre-

dictable, but typically triggered by strong emotions, usually positive, such as laughing out loud, telling a joke, making witty remarks, surprise, unexpectedly meeting a familiar acquaintance. However, it rarely occurs in response to stress, fear, or physical exertion [13]. Being a key diagnostic marker for narcolepsy, cataplexy deserves special attention from clinicians during evaluation. It may manifest in incomplete forms, affecting specific muscle groups such as facial muscles, upper or lower limbs, accompanied by dysarthria, facial flickering, sagging of the jaw, head dropping, or unlocking of the knees. Interestingly, some patients might not perceive the partial episodes as abnormal. These partial attacks can be very subtle and sometimes only recognized by experienced observers such as the patient's partner. However facial involvement is a strong diagnostic marker [10]. The duration of cataplexy is brief, it can range from a few seconds to less than two minutes. Long cataplexies are exceptional but if a trigger persists, consecutive attacks may merge to form what seems to be one long episode. A sudden withdrawal of anticataplectic medication, especially antidepressant agents (see below), can result in "status cataplecticus", with long-lasting episodes, almost continuously. The frequency may vary from infrequent occurrences (less than once a year) to multiple episodes per day. Cataplexy tends to worsen with inadequate sleep and fatigue. A transient reversible loss of deep-tendon reflexes during an attack is observed, and may help to distinguish pseudo-cataplexy, but they can persist in partial episodes [14]. Respiratory muscles are not involved. Occasionally patients may fall asleep during generalized cataplexy, particularly if the episode is prolonged.

As the diagnosis of cataplexy is usually based on clinical interview, it is crucial to define typical versus atypical cataplectic episodes. We present a list of these features in Table 1, according to previously published papers [12,15,16], and adapted from the features detailed in ICSD-3-TR [4]. Typical cataplectic attacks (with some variations of typical cataplexy), cataplexy with atypical/unusual features, specificities in children, and episodes not compatible with cataplexy are listed. We also propose a degree of certainty of cataplexy (expert opinion). It is interesting to note that a combination of typical and unusual features is possible in a patient, as well as the occurrence of both cataplectic and non-cataplectic spells as described in epileptic patients with seizures and pseudo- or non-epileptic seizures [17]. Finally, biological markers are of great interest (see below for more details: "diagnosis criteria") as cataplexy is a symptom highly associated with orexin-deficiency. Typical cataplectic attacks are, in most cases, associated with low cerebrospinal fluid (CSF) orexin levels, and presence of the allele HLA DQB1*06:02 in NT1. When the lumbar puncture cannot be performed, the absence of HLA DQB1*06:02 allele has a good negative predictive value, especially when the patient has cataplectic episodes with atypical features. On the other hand, a patient with CSF orexin-deficiency who reports cataplexy should be considered as "cataplectic", even if the episodes present with unusual features. The physician should thus consider all clinical features, then propose CSF orexin measurement as a confirmation, because one may simply have missed the whole cataplexy spectrum. It is even more questionable for patients with intermediate CSF orexin levels (between 110 and 200 pg/mL), who may be on the narcolepsy spectrum with an "incomplete form of NT1", a rare and heterogeneous condition [18]. Children have a particular phenotype described thereafter.

4.3. *Disrupted nocturnal sleep*

Disrupted nocturnal sleep (DNS) is a frequent symptom in NT1, ranking as the third most common after EDS and cataplexy, with a prevalence that varies between 30–95%, depending on the definition used. Narcoleptic patients with DNS often encounter fragmented nocturnal sleep, instability between waking and sleeping states, and they experience sudden and inappropriate shifts between these states [20], a finding observable also in children [21]. In a recent review [22], the characterization of DNS clinically and by polysomnography (PSG) revealed that the way patients describe DNS and how PSG captures it are distinct from insomnia features [23].

Clinically, nocturnal sleep can be disrupted by many conditions in NT1, variably related to orexin-deficiency. Rapid eye movement (REM) sleep abnormalities such as vivid dreams, nightmares, REM sleep without atonia (RSWA) (a persistence of muscle tone with excessive twitching during REM sleep), REM sleep behavior disorder (RBD) [24–26], hallucinations, and sleep paralysis can contribute to DNS. Non-REM sleep parasomnias, sleep-disordered breathing [27], periodic leg movements during sleep [28,29] and restless legs syndrome [30] are also responsible for nocturnal sleep disturbances. Depressive symptoms are common in narcolepsy and may be associated with sleep disturbances, but also with daytime sleepiness [31].

On PSG, DNS in NT1 is characterized by sleep instability, with frequent brief awakenings and sleep stage transitions, increased wake time after sleep onset, more stage 1, shifts to stage 1 and wake from deeper stages [32,33]. This fragmented sleep is usually associated with poor sleep quality [32]. DNS complaint in NT1 is associated with overall disease severity, several PSG parameters and objective sleepiness, and this symptom improves with treatment [34]. A study showed that an artificial intelligence (AI) algorithm could discriminate patients with NT1 by analyzing their nocturnal sleep features only [35]. In another recent study, the effectiveness of automatic AI algorithms to score sleep and extract biomarkers from hypnodensity graphs was demonstrated, particularly in distinguishing NT1 from the other disorders of hypersomnolence, with high levels of accuracy and performance [36].

4.4. *Sleep paralysis and hypnagogic/hypnopompic hallucinations*

Sleep paralysis and sleep-related hallucinations are not specific to narcolepsy, as they can also occur in the general population (at least once in a life in 20%), comorbid with anxiety [37], but they are much more frequent and more disturbing for narcoleptic patients, reported by 50% of them [9]. Sleep paralysis is an incapacity to move the limbs or head and to speak when falling asleep or waking up, lasting a few seconds or minutes. This symptom is not dangerous but can be very frightening. Sleep-related hallucinations are dreamlike auditory, visual, or tactile hallucinations occurring at sleep onset, called hypnagogic, or upon awakening called hypnopompic.

Table 1 – Typical and atypical cataplexy features and proposed related degrees of certainty. Adapted from references [15,19] and ICSD-3-TR [4], and expert opinion.

CLINICAL FEATURES

Typical cataplectic attacks

Type of attack

Either: partial loss of muscle tone (most often) and generalized loss of muscle tone (sometimes)

Or: only partial loss of muscle tone[a]

Localization

Partial: bilateral loss of muscle tone in the face, neck, or legs, especially knees, sometimes involvement of the arms

Generalized: bilateral progressive loss of muscle tone generally starts in the face or neck and builds over seconds, leading to inability to stand and sometimes a subsequent fall

Abrupt return of muscle tone after the attack

Triggers

Clear emotional triggers

Sudden positive emotions as laughter, telling a joke, making a witty remark, surprise

Less frequently: anger

Duration: brief, up to 1 min, usually < 30 seconds, classically a few seconds

Frequency: quite variable, but usually at least once per month if untreated

Consciousness preserved

For an individual cataplectic attacks are often stereotypical, but the duration and the extent of progression and extension into involved muscles may vary

Cataplectic rebound when an antidepressant agent is abruptly interrupted

Variation of typical cataplexy

Occasional spontaneous episodes (especially when the patient is sleepy, and quite common in children)

Asymmetrical attack

Facial twitching

Jerky arm movements

Rare episodes, less than one per year, if untreated

Atypical cataplectic attacks/unusual features[b]

Exclusively generalized attacks without a history of partial episodes

Hyperacute generalized muscle weakness without build-up over seconds, leading to falls and injuries

Localization

Purely unilateral

Affecting only the upper limbs and not the face, neck, or lower limbs

Prolonged recovery time of several minutes is needed to recover after a single attack

Triggers

Attacks are never triggered by laughing, mirth, or joking

Negative emotions (such as anxiety, fear, stress, sudden startling noise) as the sole triggers

Absence of clear triggering factor (except sometimes in children)

No association with emotional triggers (except sometimes in children)

Duration: long-lasting episodes in adults, of several minutes, in the absence of an ongoing precipitant

Uncertainty regarding the preservation of consciousness

Relatives and people nearby never notice the episodes

Few cataplectic rebound when an antidepressant agent is abruptly interrupted

Very unlikely cataplectic attacks – Episodes not compatible with cataplexy

Alteration of consciousness, from the start of the attack

Duration: > 10 minutes, in the absence of a precipitating trigger

Remaining deep-tendon reflexes when elicited during a generalized attack

Clear signs of attacks other than cataplexy

Typical aura experience of epilepsy

Typical prodromal signs that may be experienced during vasovagal syncope (warm feeling, sweat, dizziness, tinnitus, visual and auditory impairment, nausea, tingling sensation in the extremities)

Presence of symptoms after the episode such as alteration of consciousness, nausea, persisting muscle weakness

No cataplectic rebound when an antidepressant agent is abruptly interrupted

Specificities in children

These features are considered typical in young children

Cataplectic facies: subtle facial expressions or choreic-like movements, perioral movements such as grimacing and tongue protrusion, droopy eyelids, mouth opening

Generalized hypotonia (gait unsteadiness), or occurrence of falls in the absence of clear emotional triggers (i.e. spontaneous episodes)

Negative and active motor disturbances, with complex hyperkinetic component

Episodes not always related to emotions

Lack of awareness, movements reported by parents only

DEGREES OF CERTAINTY

Highly probable: two or more of the characteristics of "typical cataplectic attacks" are present

Probable: variations of typical cataplexy are present[c]

Possible: at least one of the characteristics listed in "atypical cataplectic attacks" is present[c]

Unlikely: one or more of the characteristics of "atypical cataplectic attacks" are present

Very unlikely: at least one of the characteristics listed in "episodes not compatible with cataplexy"

[a] Mostly involving also the facial district.

[b] It is specified in ICSD-3-TR: "if two or more of these characteristics are present, the episodes should not be labeled as cataplexy".

[c] Note the exceptions for children for some features within the "unusual" or "variation of typical" cataplexy, remaining therefore in the "highly probable category".

They can be associated with a sleep paralysis. These symptoms are abnormal expressions of REM sleep, and could be described as "intermediate" or "dissociated states" including wake-like and REM sleep-like features during with rapid transitions from wake to REM sleep, or from REM sleep to wake.

The severity of symptoms of narcolepsy, their presence, their frequency and their consequences may be assessed by validated questionnaires to monitor and optimize disease management [38].

5. Diagnostic criteria

The diagnosis of NT1 involves a clinical assessment and nocturnal polysomnography (PSG) followed by a multiple sleep latency test (MSLT). Current criteria according to the revised version of ICSD-3-TR [4] are listed in Table 2.

Nocturnal PSG is mandatory before MSLT [39], and aims to identify other potential causes of daytime sleepiness or nocturnal sleep disorders. The ICSD-3-TR specifies that MSLT must be performed in accordance with current recommended protocols (American Academy of Sleep Medicine [39]): sleep logs

Table 2 – Diagnosis criteria for narcolepsy type 1 according to ICSD-3-TR [4] (AASM, 2023).

Diagnostic criteria for narcolepsy type 1, orexin/hypocretin deficiency syndrome, narcolepsy with cataplexy: criteria A, B and C are required
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep B. The presence of one or both of the following elements 1. Cataplexy[a,b] and either a. Mean sleep latency of less than or equal to 8 minutes and two or more SOREMPs on a MSLT performed in accordance with current recommended protocols (see reference [39]) b. A SOREMP (within 15 minutes of sleep onset) on nocturnal PSG 2. CSF Orexin-A/Hypocretin-1 level, measured by RIA, is less than or equal to 110 pg/mL (using a Stanford reference sample) or less than one-third of mean values obtained in normal subjects with the same standardized immunoreactivity assay[c] C. The symptoms and signs are not better explained by chronic insufficiency sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal
[a] See paragraph "symptoms" in this review for the features of cataplexy, and Table 1 for typical and atypical features. [b] *Typical* cataplexy is most strongly associated with NT1. Although some patients with NT1/orexin-deficiency may present with *atypical* cataplexy features, presentations that include only atypical cataplexy should raise a higher index of doubt regarding NT1 diagnosis. Clinical judgment is required. [c] If orexin/hypocretin deficiency is verified, the diagnosis of NT1 should be made regardless of other comorbidities that could potentially be related to clinical symptoms, given the definitive nature of this finding.

are required, accompanied by actigraphy whenever possible, prior to in-laboratory sleep testing, to evaluate for insufficient sleep and circadian rhythm disturbances. The diagnosis of NT1 requires two or more SOREMPs (i.e., REM sleep within 15 minutes of sleep onset) on MLST, with a mean sleep onset latency of less than eight minutes. In the revised ICSD-3-TR, one SOREMP detected during the previous nocturnal PSG may replace the MSLT results showing two SOREMPs, when clear-cut cataplexy is present (Table 2). A nocturnal SOREMP is indeed very specific, in the absence of another sleep disorder, but the sensitivity is low (around 50%), hence the major importance to define properly a typical cataplexy (Table 1).

An alternative, or complementary approach to diagnosis involves measuring CSF orexin-A levels. CSF orexin levels lower than 110 pg/mL or one-third of mean normal control values in individuals with clear-cut cataplexy, is a highly specific and definite criterion for diagnosing narcolepsy. CSF orexin-A levels must be measured in duplicate using direct I^{125} radioimmunoassay (RIA) (Phoenix Pharmaceuticals, Belmont, CA), and back-referenced to Stanford reference samples (Stanford University Center for Narcolepsy, Palo Alto CA). CSF orexin-A levels $\leq$ 110 pg/mL are considered low, levels between 110 and 200 pg/mL are intermediate, and levels $>$ 200 pg/mL are considered normal [40]. It is worth noting that around 10–20% of cases do not report cataplexy but have low CSF orexin-A levels and thus are diagnosed as NT1, highlighting the importance of this test. In the past, the diagnosis of narcolepsy was supported by the presence of HLA DQB1*06:02 allele, which is found in 92% to 97% of Caucasian narcoleptics but only in 25% of the general population. However, in ICSD-3 the HLA typing was removed from the diagnostic criteria for NT1, and it is still absent in ICSD-3-TR. It can be used for its good negative predictive value when the clinical picture (especially cataplexy) is atypical [16], and if the patient refuses the lumbar puncture.

Of interest, in the previous version of ICSD-3 [41], NT1 could be diagnosed only when the symptoms were present for at least three months. This time frame was removed in the revised ICSD-3-TR, which makes sense, when clear-cut cataplexy or established orexin-deficiency are confirmed the first weeks at disease onset, as suggested in a recent position paper [16]. Alternative measures of the MSLT may also be used, and could be included in future classifications of sleep disorders. For instance, a mean daytime REM sleep duration $\geq$ 4.1 min within the first 20 minutes of the test has better sensitivity and specificity compared with standard criteria, to identify orexin-deficiency among patients with hypersomnolence [42].

6. Comorbidities

Several common comorbidities are seen in NT1, although they are not part of the diagnosis criteria. They must be taken into account when the patient is evaluated, to propose a personalized care.

Among neuropsychiatric disorders, mood disorders, anxiety disorders, suicidal thoughts [31], psychotic symptoms [43], eating disorders, and attention deficit hyperactivity disorder (ADHD) [44] (especially in children) can be seen. The high frequency of depressive symptoms supports the hypothesis of an endogenous depression.Narcolepsy shares with major depression a reduced nighttime REM sleep latency, and an increased REM sleep pressure and sleep fragmentation [45,46].

Cardiovascular and metabolic disorders are also common: overweight and obesity, type 2 diabetes, metabolic syndrome, [47,48] cardiovascular diseases (cardiac rhythm abnormalities, hypertension) [49,50] and autonomic disturbances [51]. Obesity and overweight are very frequent, approximately one-third of patients are obese, and even more in childhood narcolepsy [52,53]. The exact cause of this weight gain is unknown, but could be related to orexin-deficiency, and a distinct metabolic profile in the sera has been shown in NT1 versus controls [54]. A non-dipping blood pressure profile affects a substantial percentage of patients, estimated between 30% and 50% (a condition also observed in narcoleptic animal models), and hypertension also related to psychostimulants intake requires careful long-term monitoring [50,55]. While cardiac sympathetic innervation remains normal in NT1, patients with cardiovascular comorbidities and REM sleep motor deregulation may be at a higher risk [56]. A recent paper showed that adults with narcolepsy have a higher incidence of new-onset cardiovascular events [57,58], suggesting that physicians should carefully assess cardiovascular risk when considering treatment options.

Finally, NT1 is often associated with other sleep abnormalities. REM sleep parasomnias (RBD in 60% of patients [59,60] vivid dreams and nightmares, lucid dreams) are frequent, while non-REM sleep parasomnias (sleepwalking, sleep

terrors, enuresis) are occasionally reported [24–26]. Dissociated sleep features are observed on PSG, with mixed sleep stages and RSWA [59,61]. In contrast to idiopathic RBD (iRBD), there is no gender predominance in NT1-RBD, the age of onset is younger, and movements are less violent. Of interest, cardiac sympathetic activity and presence of deposits of phosphorylated alpha synuclein can differentiate iRBD and NT1 with RBD, suggesting a different pathophysiology [62,63]. Obstructive sleep apnea is often reported in narcolepsy, especially in adults, with a prevalence ranging from 10% to 20%, and is probably related to overweight [64]. Periodic legs movements during sleep but also during wakefulness [28,29] and restless legs syndrome [30] are quite common, with a probable different pathophysiology than primary restless legs syndrome [65].

7. Narcolepsy type 2

Initially considered as a phenotypic variation of narcolepsy with cataplexy and formerly known as ''narcolepsy without cataplexy'', NT2 is now recognized as a distinct diagnostic entity on its own. Apart from the presence of cataplexy, the clinical features are usually similar to that of narcolepsy with cataplexy, including similar EDS characteristics and associated REM abnormalities such as sleep-related hallucinations and paralysis [5]. Other symptoms such as prolonged nocturnal sleep and sleep inertia may be reported by narcoleptic patients (especially in NT2, but rarely in NT1), as components of the ''hypersomnolence phenotype'' [66].

The frequency and specific traits of DNS in NT2 are currently inadequately defined and lack comprehensive research. Indeed, to confirm the diagnosis of NT2, one should rule out nocturnal sleep disturbances likely to explain EDS. The prevalence of NT2 (when compared to narcolepsy with cataplexy) is still subject to debate, with a ratio from 2–3 to 10 [67]. However, a much higher frequency was reported in US general population [68], and a much lower frequency in European population [69]. Several sleep experts propose that NT2 may be very heterogeneous, and rather a disorder than a disease per se. A subgroup of patients would be closer to NT1 patients, while another subgroup would be close to idiopathic hypersomnia [16,70]. The clinical course of NT2 is variable. Some patients may later develop cataplexy and are thus reclassified as NT1 (also if a lumbar puncture shows low CSF orexin levels). Other patients may have a chronic stable condition, while others may improve spontaneously. A change in the phenotype toward idiopathic hypersomnia can be seen [71,72].

As in NT1, PSG followed by the MSLT is required to confirm the diagnosis (Table 2), with the presence of a mean sleep onset latency of less than eight minutes and two or more SOREMPs. A SOREMP during the previous nocturnal PSG can replace one of the SOREMPs on the MSLT. EDS and the results of the MSLT are not better explained by other causes such as sleep insufficiency, obstructive sleep apnea syndrome, delayed sleep phase syndrome, or the effect of medication or substances, or their withdrawal (which assumes that an exhaustive work-up is carried out). The association with HLA DQB1*06:02 is weaker (around 40–50% of cases) than in NT1, and CSF orexin-A levels are higher than 110 pg/mL by definition.

As mentioned above, patients with narcolepsy with intermediate orexin levels are rare, with a heterogeneous phenotype that cannot be currently named as NT1 or NT2 in ICSD-3-TR [73]. HLA DQB1*06:02 and lower CSF orexin levels are associated with typical narcolepsy features, calling for future research to distinguish incomplete from probable secondary narcolepsy forms.

As for NT1, and probably even more importantly for NT2, it is specified in the ICSD-3-TR [4] that MSLT must be performed in accordance with current recommended protocols [39]: sleep logs are required, accompanied by actigraphy whenever possible, prior to in-laboratory sleep testing, to evaluate for insufficient sleep and circadian rhythm disturbances (Table 3). Indeed, if comorbidities are ''admitted'' in NT1 diagnosis, especially when orexin-deficiency is confirmed, sleep debt is a major differential diagnosis in NT2. Note that the criteria of ''3 months of evolution of EDS'' (Table 3) was kept in the revised ICSD-3-TR, in contrast to NT1. NT2 is indeed less well-defined, with a less well-characterized clinical course, and sleep deprivation may explain PSG/MSLT findings. Among differential diagnoses, shift work and antidepressant intake deserve particular attention, being frequent condition in the general population. Alternative measures of MSLT could be also of interest, with for example REM sleep duration $\geq$ 5.7 min identifying at best orexin-deficiency among patients with narcolepsy [42]. The stability of these markers over time remains to be tested. Overall, despite

Table 3 – Diagnosis criteria for narcolepsy type 2 according to ICSD-3-TR (AASM, 2023).

Diagnostic criteria for narcolepsy type 2, narcolepsy without cataplexy: criteria A, B, C, D and E are required
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep, occurring for at least three months
B. A mean sleep latency of less than or equal to 8 minutes and two or more SOREMPs on a MSLT performed in accordance with current recommended protocols (see reference [39]). A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT[a,b]
C. Cataplexy is absent[c]
D. If CSF Orexin-A/Hypocretin-1 level is measured by RIA, it is either > 110 pg/mL (using a Stanford reference sample) or more than one-third of mean values obtained in normal subjects with the same standardized assay[d]
E. The symptoms and signs are not better explained by chronic insufficiency sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal

[a] The diagnosis value of a SOREMP on nocturnal PSG in the absence of MSLT SOREMPs is not established for NT2. However, it may help guide clinical decision-making, such as the need to pursue repeat or alternative testing.
[b] Because the circadian clock strongly gates the propensity of REM sleep, NT2 should not be diagnosed in a shift worker without prior re-entrainment to a normal schedule.
[c] If cataplexy appears later, the disorder should be reclassified as NT1.
[d] If the CSF orexin/hypocretin deficiency is measured at a later stage and found to be either less than or equal to 110 pg/mL (using a Stanford reference sample) or less than one-third of mean values obtained in normal subjects with the same standardized immunoreactivity assay, the disorder should be reclassified as NT1.

some recent advancements, NT2 is still inadequately acknowledged and understood, and further research is needed to characterize this disorder.

8. Narcolepsy in childhood, specificities in children

Some specificities are seen in children with narcolepsy. Regarding sleepiness, children may fight this symptom, leading to behavioral changes such as hyperactivity, irritability, and attention deficits (ADHD). Automatic behaviors during daytime, with continuation of activity and no memory of the event is also particularly frequent in childhood [74]. Figure 1 shows three examples of children with different phenotypes of sleepiness on MSLT and 24-hour-PSG. Cataplexy, especially when close to disease onset, may present as negative and active motor disturbances, with subtle facial expressions or choreic-like movements, perioral movements such as grimacing and tongue protrusion [19]. Cataplexy may present as facial ("cataplectic facies") or generalized hypotonia, with droopy eyelids, mouth opening, or gait unsteadiness. These phenomena are not always related to emotions. A lack of awareness of this symptomatology is common, and the movements may be reported by parents only. MSLT cutoffs are slightly different in children, with at least two SOREMPs or (instead of "and") a mean sleep latency $\leq$ 8.2 minutes on MSLT being valid and reliable markers for NT1 diagnosis [75]. In this cohort of children and adolescents, the age surprisingly did not influence MSLT results. DNS seems also frequent in pediatric NT1. The Wake/N1 index is an objective measure of DNS severity [22]. NT1 is the most frequent cause of RBD in young patients [76], it is a common sleep comorbidity in NT1 children [77]. The narcolepsy severity scale (NSS) was initially developed for adults [78], then a version for school-aged children and adolescents (NSS-P) [79] was validated. In children, especially at the onset of the disease, half of the patients are obese, and often have precocious puberty [52,53].

9. Pathophysiology: orexin/hypocretin deficiency and dysimmune process

A significant breakthrough occurred in 2000 when researchers discovered that the loss of a specific group of neurons synthesizing orexin played a crucial role in the pathophysiology of NT1 [80,81]. Post-mortem studies revealed that narcoleptic patients with cataplexy showed a selective loss of orexin cells in the lateral hypothalamus. Orexin-A and -B (also called hypocretin-1 and 2) are endogenous neuropeptides that promote arousal [82,83]. A relatively small group of approximately 70,000 to 80,000 neurons in the lateral hypothalamus have widespread projections to multiple neuronal systems. As a result, they play a crucial role in various physiological functions, including regulating the sleep/wake regulation, but also neuroendocrine and autonomic functions, the reward system, emotional behaviors and metabolism [84].

Across species, a defect in orexin signaling leads to a narcoleptic phenotype [85].Narcoleptic dogs were the first described animal model, with a mutation in the orexin-2 receptor gene [86], subsequently leading to the discovery of human narcolepsy cause [87,88].

Lack of orexin is probably the main cause of sleepiness in NT1, but several projecting aminergic neurotransmitters could also play a role. However, no striking differences among CSF monoamines, their metabolites and trace amine levels were found in narcoleptic patients and subjects without objective sleepiness [89]. A substantial increase in the number of histaminergic neurons was shown in NT1 [90], but research in mouse models of narcolepsy have yielded conflicting results regarding this increase [91]. More recently, post-mortem investigations revealed a selective decrease in corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus of NT1 patients [92]. An upregulation of activity by histamine neurons was also revealed recently by the same group [93].

The severity of EDS and cataplexy in individuals with narcolepsy may be linked to the extent of orexin neuron loss and the reduction in CSF orexin levels [94,95]. It has been hypothesized that some NT2 patients might have a partial loss of orexin neurons, indicating a continuum in pathophysiology with NT1. While most patients with narcolepsy without cataplexy have normal CSF orexin levels [96], a few individuals with NT2 were reported to exhibit a loss of orexin neurons below 50% of normal levels, a finding also observed in rodent models [94,97]. Interestingly, animal models with partial orexin loss demonstrate sleepiness but not cataplexy [98].

The exact underlying process leading to the destruction of orexin neurons remains unknown, but it is widely accepted by the scientific community that NT1 is probably an immune-mediated disease [99,100]. Its exceptionally tight association with the HLA class II allele HLA DQB1*06:02 (> 98% of NT1, with few exceptions [101]), other recent genetic evidence such as polymorphisms of T cell receptor genes, and the increased incidence after vaccination with the vaccine Pandemrix® during the 2009 H1N1 influenza pandemic also support this hypothesis [102].

The current hypothesis proposes that in individuals with a genetic predisposition, environmental triggers like viral or bacterial infections may activate CD4+ and CD8+ T cells, leading to immune activation. These T cells exhibit a proinflammatory signature with elevated levels of B-cell-supporting cytokines, ultimately resulting in the destruction of orexin cells. The search for self/foreign antigens recognized by the pathogenic T cell response in NT1 is under investigation. Increased T cell reactivity against orexin has been reported in NT1, but data demonstrating a primary role for T cells in neuronal destruction are currently lacking. Animal models of narcolepsy are providing clues regarding the roles of autoreactive $CD4^+$ and $CD8^+$ T cells in NT1 [103–107].

Conversely, the pathophysiological mechanisms underlying NT2 remain largely unknown, likely due to the heterogeneous and polymorphic nature of this disorder.

10. Treatment options and management

Despite significant advances in our understanding of the mechanisms of narcolepsy, the current treatment of narcolepsy remains currently symptomatic and lifelong treatment is necessary [108,109]. The list of currently available medications in narcolepsy is provided in Table 4. Management strategies

Table 4 – List of treatments available for narcolepsy.

Drug	Targeted symptoms	Approval by FDA and EMA	Class of evidence for use in childhood
Modafinil	EDS	FDA, EMA	No clinical trial
Armodafinil	EDS	FDA	No clinical trial
Methylphenidate	EDS	FDA, EMA	No clinical trial
Sodium oxybate	EDS Cataplexy Disturbed nocturnal sleep	FDA, EMA	Class I evidence trial, approved in children with narcolepsy by FDA and EMA for the treatment of EDS and cataplexy [110]
Sodium oxybate once at night (combination of immediate release and long release)	EDS Cataplexy Disturbed nocturnal sleep	FDA	No clinical trial
Lower-sodium oxybate (calcium, magnesium, and sodium oxybate)	EDS Cataplexy Disturbed nocturnal sleep	FDA	Approved in children with narcolepsy by FDA for the treatment of EDS and cataplexy but no specific clinical trial
Pitolisant	EDS Cataplexy	EMA (for EDS and cataplexy), FDA (for EDS)	Class I evidence trial, approved in children with or without cataplexy by EMA [111]
Solriamfetol	EDS	FDA, EMA	Ongoing international clinical trial
D-Amphetamines	EDS	FDA Approved in rare EU countries	No clinical trial
SNRI (venlafaxine, duloxetine), SSRI (fluoxetine, citalopram), tricyclic antidepressants (clomipramine)	Cataplexy	Clomipramine approved in rare EU countries	No clinical trial

EDS: excessive daytime sleepiness; EMA: European Medicines Agency; EU: European; FDA: Food and Drug Administration; SNRI: serotonin and norepinephrine reuptake inhibitors; SSRI: selective serotonin-reuptake inhibitors.

are well-codified in narcolepsy, and it is essential to consider non-pharmacological approaches, including behavioral and psychosocial strategies, alongside pharmacological interventions. Psychoeducating the patient and promoting good sleep hygiene with a regular nighttime sleep schedule, incorporating short scheduled naps throughout the day, engaging in physical activity, and promoting weight control should always be proposed. Joining a patient organization can offer valuable support, opportunities for sharing experiences, and encourage better acceptance of the disease and adherence to treatment.

Among symptomatic medication options, a single drug may target multiple symptoms, or a combination of medications may address specific symptoms one by one. Given the unique pathophysiology of NT1, one promising future alternative lies in orexin replacement therapy. Orexin receptor-2 agonists are particularly encouraging candidates for treating narcolepsy in orexin/ataxin-3 narcolepsy mice, and humans with NT1 and NT2 [112]. Very recently, a major breakthrough in this field reported near-normalization of sleepiness and cataplexy over an 8-week period in patients with NT1, but has been associated with some hepatotoxic effects [113]. Another potential approach is to prevent the destruction of orexin neurons through the use of immunomodulatory agents at the onset of NT1, with the goal of modifying its clinical course. However, attempts to utilize such therapies on uncontrolled case studies, with limited numbers of patients, have often yielded disappointing results [100].

The primary recommended approach for managing narcolepsy symptoms is through symptomatic treatments, which are supported by strong scientific evidence (level A). These treatments include the use of stimulants/wake-promoting agents to treat EDS, antidepressant agents to manage cataplexy, and sodium oxybate for both symptoms [114]. Notably, sodium oxybate has the additional benefit of improving fragmented nocturnal sleep, and also often reduces weight in obese patients. The European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) have approved most of these drugs, such as wake-promoting agents and sodium oxybate (Table 4). However, some medications are used off-label based on expert consensus only. This is the case of antidepressant agents for cataplexy, recognized for their utility despite not having formal approval for this specific indication.

Recent reviews have outlined the recommended management strategies for narcolepsy, with guidelines of the European Sleep Research Society and the American Academy of Sleep Medicine [115,116]. The first-line medications are wake-promoting agents or psychostimulants including modafinil, armodafinil (not available in Europe), pitolisant, solriamfetol, but also sodium oxybate. Modafinil and armodafinil act by increasing the extracellular concentration of dopamine through the blocking of its transporter. Pitolisant, on the other hand, is a wake-promoting agent that activates histamine neurons, acting as a selective histamine H3 receptor inverse agonist. Solriamfetol, being a derivative of phenylalanine, exhibits dopaminergic and noradrenergic activity, with a potent wake-promoting effects. Sodium oxybate, a medication taken at night and promoting slow wave sleep, acts by stimulating GABA-B receptors, leading to a modulating effect on GABAergic, noradrenergic, and dopaminergic neurons, as well as on thalamo-cortical neurons. It exhibits an effect on nocturnal sleep (and targets DNS), cataplexy, and EDS, with the maximum impact on the latter two symptoms observed

after several weeks of treatment. As for second-line medications, methylphenidate is an option, although with surprisingly limited supporting evidence. Amphetamines are considered third-line therapy for EDS due to their potential risk of abuse and serious adverse effects on psychiatric and cardiovascular health. To manage cataplexy, sodium oxybate and pitolisant are recommended as the first-line strategies. Antidepressants, including selective serotonin and dual serotonin and noradrenaline reuptake inhibitors, are widely used and highly effective with minimal side effects. Their uses are based on expert consensus, and randomized controlled trials are lacking. The effect on cataplexy is often seen at the first intake, with doses lower than those used for antidepressive purpose. An abrupt withdrawal leads to a rebound of cataplexy. A recent study showed an increased cataplexy frequency in participants tapering/discontinuing antidepressant anticataplectic for 3–10 weeks, a more prominent finding in participants taking antidepressants alone compared to those taking sodium oxybate and antidepressants [117]. Medications that effectively treat cataplexy also reduce hypnagogic hallucinations and sleep paralysis. To manage DNS, sodium oxybate proves beneficial, clearly reducing the number of nighttime awakenings and promoting increased slow wave sleep. Consequently, sodium oxybate is considered a first-line treatment for narcoleptic patients with disturbed nighttime sleep. Recent developments in sodium oxybate formulations, such as low-salt and long-acting compositions, have been recently developed for the treatment of narcolepsy, but are not yet available in Europe [118,119].

The management of EDS and REM sleep deregulation (hypnogogic hallucinations and sleep paralysis) in NT2 relies so far on the same management as in NT1.

The consequences of narcolepsy on patients' life involve both the symptoms of the disease and comorbidities [120], with impaired quality of life and increased humanistic and economic burden [121]. Although the academic and occupational outcomes do not seem to be severely altered, patients experience more difficult trajectories [122], which calls for early and comprehensive care [123].

11. Conclusion

A major advance in the field of sleep medicine was the understanding of the pathophysiology of NT1, caused by the loss of hypothalamic neurons producing orexin, a neurotransmitter regulating wakefulness and sleep, which can be measured in the CSF. Two decades later, a major breakthrough is the arrival of oral orexin receptor-2 agonists as new medications for narcolepsy [113]. NT1 is an exceptional model to study hypersomnolence and its mechanisms, but it is now crucial to gain further insights into the other and various causes of central hypersomnolence, especially the understudied disorder NT2. The novelties in ICSD-3-TR criteria may promote an earlier and more accurate diagnosis of NT1 and NT2. It is essential to enhance personalized and precision medicine approaches for these patients, not only at the pharmacological level but also by considering a comprehensive approach that addresses the educational, social, and occupational requirements.

Disclosure of interest

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