Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts

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Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts.

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For all authors: there are no conflicts of interest related to this review
Keywords

Sleep, Classification, Diagnosis, Hypersomnolence, Hypersomnia, Excessive daytime sleepiness, Narcolepsy, Cataplexy, Fatigue, MSLT
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<td>AHI</td>
<td>Apne–Hypopnea Index</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>EAN</td>
<td>European Academy of Neurology</td>
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<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immuno Sorbent Assay</td>
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<tr>
<td>ENS</td>
<td>Excessive need for sleep</td>
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<tr>
<td>ESRS</td>
<td>European Sleep Research Society</td>
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<tr>
<td>ESS</td>
<td>Epworth sleepiness scale</td>
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<td>EU-NN</td>
<td>European Narcolepsy Network</td>
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<tr>
<td>HH</td>
<td>Hypnagogic hallucinations</td>
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<tr>
<td>HLA</td>
<td>Human leucocyte antigens</td>
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<tr>
<td>ICSD/ICSD3</td>
<td>International classification of sleep disorders / 3rd edition</td>
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<td>IH</td>
<td>Idiopathic hypersomnia</td>
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<tr>
<td>MSLT</td>
<td>Multiple sleep latency test</td>
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<td>NT1</td>
<td>Narcolepsy type 1</td>
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<tr>
<td>NT2</td>
<td>Narcolepsy type 2</td>
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<tr>
<td>OSA</td>
<td>Obstructive sleep apnea</td>
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<tr>
<td>PLMS/PLMD</td>
<td>Periodic limb movement syndrome / Periodic limb movement disorder</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>PVT</td>
<td>Psychomotor vigilance test</td>
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<tr>
<td>RBD</td>
<td>REM sleep behaviour disorder</td>
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<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
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<tr>
<td>RLS</td>
<td>Restless legs syndrome</td>
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<tr>
<td>SART</td>
<td>Sustained attention to response task</td>
</tr>
<tr>
<td>SOREM</td>
<td>Sleep onset REM episode</td>
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<tr>
<td>SP</td>
<td>Sleep paralysis</td>
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The aim of this European initiative is to facilitate a structured discussion to improve the next edition of the International Classification of Sleep Disorders (ICSD), particularly the chapter on central disorders of hypersomnolence.

The ultimate goal for a sleep disorders classification is to be based on the underlying neurobiological causes of the disorders with clear implication for treatment or, ideally, prevention and or healing. The current ICSD classification, published in 2014, inevitably has important shortcomings, largely reflecting the lack of knowledge about the precise neurobiological mechanisms underlying the majority of sleep disorders we currently delineate.

Despite a clear rationale for the present structure, there remain important limitations that make it difficult to apply in routine clinical practice. Moreover, there are indications that the current structure may even prevent us from gaining relevant new knowledge to better understand certain sleep disorders and their neurobiological causes.

We suggest the creation of a new consistent, complaint driven, hierarchical classification for central disorders of hypersomnolence; containing levels of certainty, and giving diagnostic tests, particularly the MSLT, a weighting based on its specificity and sensitivity in the diagnostic context.

We propose and define three diagnostic categories (with levels of certainty):

1/ “Narcolepsy” 2/ “Idiopathic hypersomnia”, 3/ “Idiopathic excessive sleepiness” (with subtypes)
Introduction

The goal of a classification

The ultimate goal for a sleep disorders classification is to be based on the underlying neurobiological causes of the disorders with clear implication for treatment or, ideally, prevention and healing.

Currently, most sleep specialists refer to the International Classification of Sleep Disorders 3rd edition (ICSD3), published in 2014 to diagnose and classify sleep disorders [1]. This classification inevitably has important shortcomings, largely reflecting the lack of knowledge about the precise neurological mechanisms underlying the majority of sleep disorders we currently delineate. Despite a clear rationale for the present structure, there remain important limitations that make it difficult to apply in routine clinical practice. Moreover, the current structure may prevent us from gaining relevant new knowledge to better understand certain sleep disorders and their neurobiological causes.

This “position paper” addresses sleep disorders in adults and discusses shortcomings in the approach and structure of the ICSD3 in general with subsequent focus on the chapter: “Central disorders of hypersomnolence”. By dissecting the inconsistencies and shortcomings of the current classification, and taking into account recently obtained knowledge, we produce suggestions for an adjusted and updated section on hypersomnolence.

The aim of our “position paper” is primarily to facilitate discussions in order to:

1. improve a new version of the classification for practical use
2. define a research agenda in this area, aiming to explore further neurobiological causes and substrates for sleep-wake complaints and their underlying disorders

General comments on the current ICSD3 classification

Some of our comments on the chapter “Central disorders of hypsomnolence” deal with the general structure:

- For the classification of some disorders, such as insomnia and restless limb syndrome (RLS), the diagnosis is based solely on subjective complaints whereas for others, such as narcolepsy type 1, it presumes a precise pathophysiology. In others such as obstructive sleep apnea (OSA), diagnosis can be solely defined by findings on ancillary investigations (i.e. AHI).

- There are no levels or grades of certainty defined for the various diagnoses.

- There are hardly measures of severity for sleep-related symptoms included.

- Several potentially important assessments that can be clinically useful and easy to apply are not listed as mandatory in confirming or refuting diagnoses, largely due to problems of reimbursement in many countries including the US. Examples include actigraphy, hypocretin measurements, and HLA typing.

Comments on the chapter “Central disorders of hypsomnolence”

Terminology and consistency

- The chapter is titled “Central disorders of hypsomnolence” but contains a variety of disorders such as “Insufficient Sleep syndrome” that generally have no “central” cause, but
are primarily related to behaviour or lifestyle. In contrast, OSA as one of the most prevalent causes of hypersomnolence is not listed although it may be argued that there is usually no central origin for OSA.

It is presumed that introducing the word “Hypersomnolence” in ICSD3, after its introduction in DSM-5 in 2013 [2], was intended to solve previous inconsistencies around other similar terms such as “excessive daytime sleepiness”, “hypersomnia”, and “excessive sleepiness”. However, it has led to potential further confusion as “hypersomnolence” is used to describe both the symptom of “excessive sleepiness” and to define a group of disorders: “Central disorders of hypersomnolence”. This chapter then documents disorders such as “idiopathic hypersomnia” but not, for example, “idiopathic hypersomnolence” or “Idiopathic excessive sleepiness”. “Hypersomnolence” as defined in the DSM-5 is very similar to what used to be the definition of “hypersomnia”. Compared to ICSD3, it covers a larger variety of possible expressions of daytime sleepiness including an increased need for sleep, but it is confusing that it is used only to describe expressions of “Hypersomnolence disorders” and is not meant to be applied to narcolepsy although narcolepsy may have largely overlapping expressions.

From their original meanings, excessive daytime sleepiness (EDS) and hypersomnia are qualitatively different complaints [3-5]. This is not taken into account in ICSD3 and the distinction is blurred by use of the term “Hypersomnolence”. In this manuscript, we use “hypersomnolence” as an overarching description for the presence of EDS and/or excessive need of sleep (ENS) or an increased quantity of sleep (see also the definition section).

Hypersomnolence is not just characterized by “daily episodes of an irrepressible need to sleep or daytime lapses into sleep” as in the definition described by ICSD3. The term usually harbours much more in the way of disabling symptoms. Accordingly, it often includes impaired vigilance or sustained attention; automatic behaviours; cognitive complaints,
especially linked to poor memory; and it can be accompanied by increased need for sleep and severe sleep inertia [6-8].

- An increased need for sleep as a separable symptom is not defined. There is also no clarification in distinguishing it from clinophilia: the tendency to remain in bed in a reclined position without increased actual sleep time when objectively assessed.

- There is no explicit statement about the difference between fatigue and hypersomnolence. Fatigue may accompany EDS and hypersomnia, but it is a qualitatively different complaint and never a (core) symptom of a disorder of hypersomnolence, although it may accentuate the impairment caused by it [9].

- As mentioned, attentional problems may be an expression of hypersomnolence. However, there is no guidance as how to separate conditions considered to be “pure” attention deficit disorders such as attention deficit hyperactivity disorder (ADHD) from complaints of attention deficit as an expression of a disorder of hypersomnolence [10].

**Diagnostic criteria and tests**

- There are no clear criteria to assess or measure sleep deprivation and circadian rhythm disturbances as potential causes for hypersomnolence although it is stated that they should be excluded before making the diagnosis of idiopathic hypersomnia, for example.

- The current classification relies heavily on the MSLT result despite the test having low sensitivity and specificity for diagnostic purposes [11-13]. Moreover, more recently, the consistency of the MSLT result over time is suggested to be unreliable for several diagnoses (see also below) [14-16].

- The ability of the MSLT to quantify sleepiness has only been validated in healthy volunteers with different degrees of sleep deprivation [17-20]. It is, therefore, questionable whether it is
justified to base diagnostic categories heavily depending on MSLT results [17] and not taking age effects into account [21].

- In clinical practice, it is not uncommon for a single patient to have multiple potential causes or contributors of hypersomnolence, including sleep deprivation, OSA, and depressed mood as common examples. It would be helpful to include a paragraph in the classification regarding this issue. This highlights our lack of knowledge on the difficult question of whether depression is a primary cause of hypersomnolence in individual patients, especially given how in many, it fuels symptoms of insomnia [22-24].

- It is inconsistent that depression may be comorbid in narcolepsy type 1 but must be excluded in type 2 and idiopathic hypersomnia.

- It is not clear why narcolepsy type 1 should be diagnosed only when the symptoms are present for at least 3 months when within this period there is clear-cut cataplexy or established hypocretin deficiency.

**Relevant new knowledge and remaining unsolved issues**

**New knowledge**

- It is known for many years that the sensitivity and specificity of MSLT criteria as used in ICSD3 are acceptable in narcolepsy type 1 and, importantly, appear relatively consistent over time [14-16, 25]. In contrast, and assessed in more recent studies, the test’s sensitivity, specificity and particularly consistency over time are much less secure for the currently defined disorders: narcolepsy type 2, IH and chronic sleep deprivation[14, 25, 26].
Recent studies indicate that the sequence of sleep stages as assessed during MSLT testing may have diagnostic significance [26-28]. REM sleep occurring before stage 2 sleep is indicative of narcolepsy type 1, for example. It may be diagnostically very helpful to observe video footage of provoked cataplexy although this approach is clearly labour intensive and only suitable for patients with frequent cataplexy attacks [29, 30]. There are indications that prolonged sleep recordings and observations may offer additional diagnostic information and improve classification. However, the expense and labour intensive nature of prolonged recording is likely to limit overall acceptance and standardization of results may be difficult [31].

Issues to be solved in a new classification of Sleep-Wake disorders

It remains unclear how chronic sleep deprivation can reliably be assessed or excluded as a relevant factor. Actigraphy may be helpful but criteria and protocols for assessing the effects of sleep extension, for example, are lacking. It is also unclear how circadian disorders should be reliably assessed or ruled out as causes for EDS in the absence of precise criteria and diagnostic protocols. As currently defined, it is very likely that the currently defined disorder IH is a heterogenous entity. It appears sensible to separate a phenotype with an increased need for sleep from a phenotype without [3-5]. It is unclear whether the currently defined disorders IH and narcolepsy type 2 are always separable entities [32]. Moreover, it is not known if EDS in narcolepsy type 2 can be distinguished reliably from expressions of chronic sleep deprivation and narcolepsy type 1 [14, 26, 33].
We know that narcolepsy with cataplexy can start as narcolepsy without cataplexy but we have poorly identified reliable predictors which might include HLA typing (DQB1*06:02). Currently, only hypocretin deficiency is known to be associated with a risk of subsequent cataplexy [34].

- Narcolepsy type 1 & 2, and IH are currently largely defined and separated by MSLT criteria. We know that the result of the MSLT may change over time particularly in narcolepsy type 2 and IH. However, the contributory effects of different levels of sleep deprivation, including night shifts, in the days and weeks before the individual test is performed are unknown. To clarify if the MSLT is, indeed, a relatively inadequate test for accurately diagnosing central disorders of hypsomnolence, we must first establish guidelines how to exclude sleep deprivation in the week(s) before performing a MSLT.

- Given the current importance of the MSLT in defining whether a subject suffers from IH or narcolepsy type 2, changes in MSLT results over time will effectively change a diagnosis, even if the clinical picture is stable.

- Mindful that the sensitivity and specificity of the MSLT is low for IH and narcolepsy type 2, we should allow a different approach in future classifications for patients who have genuine complaints of hypsomnolence but fail to have diagnostic MSLT results.

- There is a need for an international standardization for measuring hypocretin levels.

In order to solve most of the issues raised, a new consistent, complaint driven, hierarchical classification, containing levels of certainty, and giving diagnostic tests, particularly the MSLT, a weighting based on its specificity and sensitivity in the diagnostic context is proposed.
Methods

A European Task Force to develop an updated guideline for the treatment of narcolepsy, endorsed by the European Neurological Association (EAN), the European Sleep Research Society (ESRS) and the European Narcolepsy Network (EU-NN), was established in 2017. Besides primary discussions concerning treatment and management of narcolepsy, issues were raised concerning diagnostic uncertainties when applying the ICSD3 during initial meetings in Lugano (2017), Montpellier (2018), Boston (2018), and Bern (2019). The current paper summarizes these discussions and conclusions. Regarding the provided definitions and recommendations: they are all ultimately based on consensus and expert opinion, but for all PubMed searches (period 1979 – April 2019) have been performed first (by GJL, CB and YD), using the respective appropriate searching terms. “Excessive sleepiness”, “Daytime sleepiness”, “Hypersomnolence”, “Hypersomnia”, “Cataplexy”, “Narcolepsy AND diagnostic criteria”, Idiopathic hypersomnia AND diagnostic criteria”, “Multiple Sleep Latency Test”, “Sustained attention AND sleep”, “Fatigue”, “Automatic behaviour”, “Clinophilia”, “Sleep inertia”, Sleep drunkenness”, “Sleep attack”, “Long sleeper”, “Hypocretin”, ”Orexin”, “HLA narcolepsy”, “Narcolepsy biomarkers”, If recommendations are solely based on expert opinion it is explicitly stated in the text. The three main authors (GJL, CB, YD) prepared a first, second and third draft which were then sent for review and revised by the task force. Consensus on all statements could be reached.

The approach

There is a focus on:
- Expressions of hypersomnolence as a specific symptom, and on cataplexy as specific marker for the only central disorder of hypersomnolence with an established cause, namely, hypocretin deficient narcolepsy.

- Other symptoms such as hypnagogic hallucinations and sleep paralysis are not considered in depth given their low diagnostic specificity for any particular cause of hypersomnolence.

- Adults.

**Principles:**

- *First:* we provide full definitions for the various concepts discussed.

- *Second:* the primary complaint of the patient is the starting point of any diagnostic process.

- *Third:* the potential multiple dimensions of the complaint of hypersomnolence are taken into account.

- *Fourth:* severity of complaints and degrees of certainty of a particular diagnosis are taken into account.

- *Fifth:* relevant new knowledge obtained after the publication of the ICSD3 in 2014 is taken into account, particularly regarding MSLT data

- *Sixth:* with the exception of narcolepsy type 1, we advocate a hierarchical approach to the diagnostic process by first excluding sleep deprivation, then sleep apnea and subsequently circadian rhythm disorders before considering a diagnosis of hypersomnolence

- *Seventh:* a diagnosis may shift to different levels of certainty or categories over time, depending on changes in symptoms or the results of additional diagnostic tests.
Definitions (alphabetical)

Problems of attention: difficulties with sustaining a purposeful focus on stimuli.

Automatic behaviours: behaviours that are performed without conscious knowledge or full voluntary control.

Clinophilia / high levels of bed rest: the tendency to spend prolonged amounts of time reclined in bed without objective evidence for increased sleep time.

Excessive daytime sleepiness (EDS)*: the complaint of an inability to stay awake during the normal wake period of the day.

Excessive need for sleep (ENS)**: the complaint of a need for an excessive quantity of sleep over the full 24 hours period. At least 10 hours of sleep are needed over 24 hours of the day with the nocturnal component providing at least 9 hours. The complaint for increased need for sleep must be, associated with impairment and distress related primarily to deteriorated quality of daytime wakefulness, and cannot be (fully) resolved by increasing the amount of sleep.

Fatigue: the complaint of physical and/or mental exhaustion with difficulties in initiating or sustaining voluntary activities that are not significantly improved by increased rest or sleep.
Hypersomnia: the objectified complaint of ENS. An objective assessment of an excessive quantity of sleep: at least 10 hours of sleep duration over 24 hours of the day with the nocturnal component providing at least 9 hours of sleep duration.

Hypersomnolence: the presence of a complaint of EDS and/or ENS.

Long sleeper: a person with a constitutional need for more sleep than average, reflected in a habitual long nocturnal sleep period of up to 12 hours in the absence of daytime complaints when this amount of sleep is fully achieved.

Nap: a short period of sleep during the wake period of the day

Sleep attack: a relatively sudden occurring unintended nap, not preceded by a feeling of sleepiness.

Sleep deprivation: a situation in which a person is not achieving a sufficient amount of nocturnal sleep as determined by their individual constitutional requirements.

Sleep inertia and drunkenness: the complaint of difficulty in achieving complete wakefulness at the end of a sleep period, potentially accompanied by confusion, disorientation, and poor motor coordination or even ataxia. Sleep drunkenness is considered as a severe manifestation of this phenomenon [8].

Unintended nap: an episode of irresistible sleep, which may occur at any time during the wake period of the day, but most commonly associated with tedious or monotonous activities.
This is the definition of the core problem. It must be acknowledged that EDS has multiple dimensions as explained in chapter 1.1.1.

The cut-offs of 9 respectively 10 hrs are based on expert opinion. They are supported by several publications and the DSM-5 and the previous edition of the ICSD [2, 35, 36]. However, additional knowledge is needed. Large data sets such as the Database of the European Narcolepsy Network that also includes information on other hypersomnolence disorders may provide these data in the near future. Machine learning could support delineation of cut-off scores [37].

The cut-off score is expert opinion. It is highly unlikely that a completely healthy person will need more than 12 hrs of nocturnal sleep.
Results

The result of applying the first four principles is described below. The clinical phenotyping results from history taking rather than from the use of questionnaires.

1) Hypersomnolence

Hypersomnolence may present in two forms, EDS and ENS.

1.1.1 Manifestations of excessive daytime sleepiness (EDS)

Clinical symptoms/complaints:

1) The presence of a feeling of daytime sleepiness throughout most of the day as opposed to symptoms of fatigue

2) Inability to stay awake in monotonous situations with unintended napping and possibly sleep attacks

3) Acquired need for scheduled napping during the day

4) Difficulty with sustained attention and vigilance

5) Automatic behaviours that can be attributed to EDS

EDS often is accompanied by cognitive difficulties, particularly memory complaints, and emotional difficulties, including irritability and distractibility. Headache complaints are also likely to be commoner.
Criteria for presence of EDS:

There is a daily or near daily presence of symptom 2 OR there is the daily presence of symptom 1 and at least one of the other symptoms listed.

1.1.2 Manifestations of excessive need for sleep (ENS) in adults

Clinical symptoms/complaints:

1) An increased need for sleep in normal daily life. The need must comprise at least 10 hours of sleep per 24 hours and/or at least 9 hours of nocturnal sleep* AND

2) The presence of at least one of the listed symptoms of EDS and/or the presence of sleep inertia/sleep drunkenness, AND

3) Sleep extension will not (fully) eliminate the symptoms/complaints of 2.

Criteria for presence of ENS:

There is a daily or near daily presence of all three listed symptoms/complaints.

* The defined cut-offs are based on expert opinion and in line with definition used in DSM-V.

1.2.1 Severity of EDS

Subjective assessment

1) For example the score on the Epworth Sleepiness Scale

2) Frequency of voluntary and involuntary naps (per day/per week)
3) Presence of complications that can be attributed to EDS (cognitive symptoms, lapses, accidents)

Of note: the presence of co-morbid fatigue may increase the burden of EDS.

Objective assessment

1) Mean sleep latency by MSLT <2-5 min; 5-8 min; > 8 min)
2) Results of vigilance test (SART)

1.2.2 Severity of ENS

Subjective assessment

1) Total number of hours sleep needed over 24 hours when given the full opportunity to sleep as compared to the amount of sleep normally obtained in the pre-symptomatic period
2) frequency/duration of inertia/sleep drunkenness following a nocturnal sleep period and a nap

Objective assessment

1) the amount of sleep per 24 hours as estimated with two weeks of actigraphy/sleep log and confirmed by a ambulant PSG recording of at least 24 hours allowing ad libitum sleep, or at least 24 hours clinical PSG recording in standardized conditions also allowing ad libitum sleep [31].*
* This recommendation is expert opinion supported by the referred study.

2) Cataplexy

2.1.1 Presence of typical or unambiguous partial cataplexy (history taking*) [38-42]

1. Bilateral loss of muscle tone in face, neck or legs (buckling knees), with or without involvement of the arms, in the absence of falls or collapse

2. Events triggered by sudden emotions, particularly of a positive nature related to mirth. Typical situations include laughing out loud or telling an amusing story/joke; making a witty remark; or pleasant surprise when unexpectedly meeting a familiar acquaintance. Other situations include weakness induced by orgasm or occasionally anger. It is most reliably diagnosed if triggers other than laughter can be identified given the significant number of healthy people who report a degree of generalised weakness induced by laughter, particularly in the legs [40, 42].

3. Duration of episodes from about a second up to 1 minute for a single attack, typically less than 30 seconds. Sequential attacks caused by a persisting precipitant trigger may have a much longer duration.

4. Preserved level of consciousness

5. Abrupt return of muscle activity after the attack

6. It is very common to have a second attack in the months after an initial episode unless treatment immediately started

2.1.2 Presence of typical or unambiguous generalized cataplexy (history taking*) [38-42]

1. Bilateral progressive loss of muscle tone generally starting in the face or neck and building up over seconds, leading to a fall to the ground with buckling of the legs
2. Events triggered by sudden emotions, particularly of a positive nature related to mirth. Typical situations include laughing out loud or telling an amusing story/joke; making a witty remark; or pleasant surprise when unexpectedly meeting a familiar acquaintance. Other situations include weakness induced by orgasm or occasionally anger. It is most reliably diagnosed if triggers other than laughter can be identified given the significant number of healthy people who report a degree of generalised weakness induced by laughter, particularly in the legs [40, 42].

3. Duration of an episode typically lasts several seconds and up to 2 minutes. In exceptional cases, sequential attacks may have a much longer duration.

4. Preserved level of consciousness

5. Abrupt return of muscle activity after the attack

Supportive criteria [40]:

- Quick clinical response to anti-cataplectic drugs, particularly antidepressants such as clomipramine or venlafaxine
- Muscle tendon areflexia/H-reflex suppression, particularly during generalized episodes [41-43].

Compatible with typical cataplexy (if criteria above are also met) [39, 40]:

- Occasionally spontaneous episodes
- Facial twitching
- Prolonged episodes after discontinuation of anti-cataplectic drugs (except sodium oxybate)
- Attacks experienced as asymmetrical but not strictly unilateral
A generalized attack may occasionally result in a full-blown sleep episode.*

There is debate whether cataplectic attacks always start in the neck and face, and also if muscle jerking or twitches are part of the typical clinical picture of cataplexy although observations made by experts lend support to this view. However, since we rely on history taking and not all patients experience these observations, these elements are not part of the mandatory criteria.

2.2 Severity of cataplexy

By history

1) Frequency of cataplexy episodes with ranges typically quantified as less than 1 per month to more than 5 per day [44]

2) Typical duration of episodes

3) Presence or absence of generalized attacks (e.g. associated with falls)

4) Subjective levels of disability caused by episodes of cataplexy, taking into account the typical situations in which they occur (e.g. at workplace)

2.3 Certainty of typical cataplexy

- The optimal method for confirming the presence of cataplexy relies on direct observation by an experienced clinician in real life or, more typically, from recorded video material [29, 30].

- Unfortunately, direct or recorded observations are rare to witness in adult patients and reliance is placed on accurate history taking. Only descriptions fulfilling all characteristics above can be considered as typical cataplexy.
Cataplexy should still be considered, but as *atypical*, if the patient reports one of the following features during history taking:

- attacks are purely unilateral or unusually prolonged in the absence of the precipitant (> 3 min)
- no clear precipitants for episodes or if only negative emotions act as triggers
- it is uncertain whether consciousness is fully preserved
- hyperacute generalised muscle weakness without build-up over seconds, leading to falls and injuries.
- only generalized attacks
- it takes minutes or longer to recover after a single attack

If more than one of the above listed characteristics is present the attacks must be considered to be “cataplexy-like” attacks. In all such cases, the measurement of hypocretin-1 in CSF may be helpful, as presence of low hypocretin favours presence of cataplexy and high levels of hypocretin decreases probability of cataplexy.

- Cataplexy is generally excluded if there is no doubt that loss of consciousness or awareness occurs at the onset of episodes.
3) Proposal for a new classification of central disorders of hypersomnolence in adults

We believe the current ISCD3 guidelines on central causes of hypersomnolence have created a degree of diagnostic confusion by:

- not consistently taking the symptomatic complaint of the patient as a starting point
- not emphasising the importance or impact of chronic sleep deprivation in the clinical assessment of hypersomnolence and its influence on the results of ancillary investigations
- incorporating the detailed results of the MSLT as primary diagnostic criteria for certain categories of hypersomnolence

The exaggerated and arguably unjustified central role for MSLT results to influence diagnosis has over-shadowed the importance and relevance of detailed clinical characteristics in disorders causing hypersomnolence. Moreover, it has stifled the search for updated and more accurate diagnostic strategies.

We argue that progress will depend on more descriptive diagnostic categories that permit changes in MSLT results over time without necessarily producing differing diagnostic labels. We would also advocate the introduction of “probable” diagnoses when the MSLT result is intermediate and potentially alternative explanations or diagnoses such as chronic sleep deprivation, OSA and circadian disorders after these have been adequately addressed. However, we advocate to avoid the use of “possible” diagnosis to prevent confusion for patients and health insurance companies (a diagnosis labelled as “possible” might be interpreted to be uncertain or unclear). Finally, it should be acknowledged that problems of sustained
attention or vigilance may be the most disabling aspects of patients with hypersomnolence, as opposed to sleepiness per se.

With the previous discussions in mind, we now propose a new classification for disorders of hypersomnolence that is aimed to improve diagnostic clarity and our understanding of disorders causing hypersomnolence. Moreover, it will facilitate treatment pathways for those who suffer from complaints of hypersomnolence in whom MSLT results have not necessarily fulfilled strict diagnostic criteria and in whom sleep deprivation has been satisfactorily excluded.

When OSA, chronic sleep deprivation and circadian rhythm disorders have been effectively excluded, we suggest the creation of three diagnostic categories, with levels of certainty, for central disorders of hypersomnolence:

1. “Narcolepsy” replacing NT1 and NT2
2. “Idiopathic hypersomnia”
3. “Idiopathic excessive sleepiness”

Only for narcolepsy are there criteria proposed for primary (idiopathic), familial, secondary (symptomatic), and narcolepsy plus (hereditary forms with additional neurological symptoms) forms [45]. We suggest discontinuing entities such as “hypersomnia due to medical disorder”, “hypersomnia due to substance abuse”, or “hypersomnia associated with a psychiatric disorder”, because in most cases it is generally unknown if the relationship is truly causal or simply co-morbid [22, 24]. Instead, medical disorders and psychiatric disorders including substance abuse are considered and listed as possible co-morbidities. This is in line with the
decision made in ICSD3 to allow to diagnose insomnia independently from the presence of a mental disorder, a medical condition, or drug or substance intake.

We suggest no changes to the diagnostic criteria for Kleine-Levin syndrome because we focus on chronic disorders characterized by persistent and not remittent hypersomnolence.

3.1 Diagnostic criteria for narcolepsy

**Level 1**

**A.** Definite

EDS and or typical cataplexy and CSF hypocretin deficiency*

**B.**

EDS with typical cataplexy and MSLT**: SL < 8 min and > 1 SOREM (including nocturnal sleep)

**Level 2**

**A.** Probable

EDS with typical cataplexy and MSLT**: either SL < 8 min or > 1 SOREM (including nocturnal sleep)

**B.**

EDS without typical cataplexy, but with HH and or SP and or disturbed nocturnal sleep; MSLT**: SL < 5 min and > 1 SOREM or SL < 8 min and > 2 SOREMs (including nocturnal sleep) & HLA DQB1*0602 positive*; other causes of EDS need to be excluded¶.

**Familial***

- EDS with cataplexy or cataplexy-like episodes****; MSLT*: SL < 8 min and > 1 SOREMP, and or hypocretin deficiency; At least one first degree family member with similar complaints including cataplexy.

**Symptomatic or secondary***

- EDS with cataplexy or cataplexy-like episodes****; the subject is known to suffer from Niemann Pick type C, Prader-Willi syndrome, or
has a demonstrated lesion in the hypothalamus [45, 46]. MSLT*: SL < 8 min and > 1 SOREMP, or hypocretin deficiency

* Hypocretin deficiency is considered both the primary cause and most specific biological marker for narcolepsy with cataplexy. The presence of hypocretin deficiency in an individual is key to determining the level of certainty in this diagnostic classification. Category 1A is therefore the most certain category. When applying the strict interpretation of typical cataplexy which is mandatory, 98% of the category 1B patients will be hypocretin deficient (familial en secondary cases excluded, see below).

Hypocretin-1 measurement in the CSF, by adjusted radio immune assay (RIA), is by far the most specific and sensitive test to diagnose narcolepsy with (typical) cataplexy [47]. By definition it is diagnostic for narcolepsy type 1 [1]. For the Stanford group, and those who adjust to Stanford values by using Stanford reference samples, the cut off is 110 pg/ml. In a clinical context, a value below this concentration is considered diagnostic. Intermediate hypocretin-1 levels between 110-200 pg/ml cannot exclude the diagnosis but there are currently not enough data to alter cut off levels to higher than 110 pg/ml. New methods of measuring CSF-hypocretin for example by mass spectrometry are under development. Currently, the mentioned cut-off points cannot be used in ELISA-based methods, which may show abnormally low values, and hence falsely positive results.

In non-familial and non-secondary cases of narcolepsy type 1, 98% are HLA DQB1*0602 positive [48]. In narcolepsy type 2, this percentage is much lower, averaging 40 to 50%. However, in the group of narcolepsy type 2, HLA DQB1*0602 positivity is nearly always seen if there is subsequent hypocretin deficiency or symptoms of cataplexy [34]. In the general population, the presence of HLA DQB1*0602 is 15 – 38% [48, 49]. Therefore, the presence of HLA is not helpful as a primary diagnostic tool but can provide evidence to exclude it and for predicting eventual hypocretin status.

Typical cataplexy is the clinical hallmark of narcolepsy type 1. It is therefore very important to define typical cataplexy as precise as possible. For this reason chapter 2 was added.
Additional support for hypocretin deficiency, beyond the presence of (typical) cataplexy:

Subjective symptoms:
- ESS >14 [39, 45, 50]
- frequent daily naps that are typically short, refreshing and associated with dream content [38, 45]

Objective testing:
Considered to be “proven” support:
- MSLT: mean SL < 5 min [34, 51]
- at least 2 SOREMPs [34]
- sleep stage sequence[27, 52-54]
- Short REM sleep latency nocturnal sleep (< 15 min) [55]. The evidence is strong in one study but there has never been an independent confirmation and the specificity for narcolepsy type 1 was very high but much less for hypocretin deficiency. Moreover, the sensitivity of this finding is low.
- Consistent abnormal MSLT findings when repeating the MSLT
Suggested support but needs better validation:
- absolute REM sleep latency MSLT < 6 min [27, 37]
- sleep stage sequence (REM sleep before occurrence stage 2 sleep or frequent transition REM to stage 2) [27, 52, 53]
- Relevant findings on a group level that need replication and validation to be added as diagnostic criteria are: sleep stage sequence/transitions in nocturnal sleep [53, 56] distribution of eye movement during sleep stages [57], and power spectra analyses [58, 59].

** For an accurate interpretation of the MSLT, age should be taken into account [15, 21]

*** In familial and secondary cases, both the presence of HLA DQB1*0602, and hypocretin deficiency in the CSF are less prevalent when compared to the idiopathic cases [60, 61].

**** For definition, see 2.3

¶ Diagnoses to be excluded are chronic sleep deficiency, circadian rhythm disorders and OSA.
It is important to realize that there is a hierarchy. First exclude sleep deprivation as cause of the complaints. If the complaints disappear after sleep extension, the complaint is cured and
the diagnostic process is completed. If the complaint remains, circadian rhythm disorders and OSA need to be excluded or treated when they might be responsible for the complaint. Only after completing these steps, and a remaining complaint that qualifies for narcolepsy level 2B, the diagnostic process to assess whether the diagnostic criteria for narcolepsy level 2B are met can be started. Symptoms must be present daily for at least 3 months,

Narcolepsy phenotype [45]
- acute
- progressive
- chronic-stable
- chronic unstable
- other

Narcolepsy aetiology [45]
- idiopathic (sporadic)
- familial
- secondary (symptomatic)
- narcolepsy plus (hereditary forms with additional neurological symptoms)

Severity of narcolepsy*
To be taken into account
- severity score of EDS (see 2.1.2)
- severity score of cataplexy (see 2.2)
- severity score for disturbance nocturnal sleep including the severity of HH and or SP
- quality of life score
- score for severity of comorbidity

* a severity score has been suggested which could be elaborated on [62].

Frequent co-morbidities of definite and probable narcolepsy in adults [45]
- Sleep disorders/disturbances: sleep disordered breathing, RLS/PLMS, RBD, other parasomnias
- Medical disorders/disturbances: obesity, diabetes mellitus type 2, autonomic instability and cardiovascular disorders
- Psychiatric disorders/disturbances: anxiety, depression, psychosocial problems

### 3.2 Diagnostic criteria for idiopathic hypersomnia

By definition, sleep deprivation as primary cause is excluded. Sleep apnea as cause needs to be excluded and in case of doubt, first be treated.

#### Level 1

**Definite IH***

1. The presence of ENS
2. The ENS complaint is acquired**
3. There is objective evidence for increased sleep need using actigraphy and PSG***

#### Level 2

**Probable IH***

1. The presence of ENS
2. The ENS complaint is acquired**
3. There is objective support for increased sleep need using actigraphy and PSG***

* The complaint must be present daily for at least 3 months and all 3 criteria must be fulfilled.
Fatigue may be present but the excessive need for sleep must be the most prominent complaint. There should be no concomitant major systemic symptoms or factors such as fever or severe pain as these may indicate chronic inflammatory conditions, infection, or autoimmune disorders. It is uncommon that the disorder develops in or after middle-age.
Depression may be present and it is often appropriate to document it as a co-morbidity.
** The point at which symptoms start or even if the disorder is truly acquired may be difficult to establish when ENS is reported in (early) childhood [5, 63].

*** For level 1, the criteria for objective confirmation are (both must be fulfilled): 1. Actigraphy with sleep logs (2 weeks): strongly supports > 9 hours sleep per night or > 10 hours sleep over 24 hrs on the majority of days, and 2. PSG recording (performed at end actigraphy recording); preferably > 19 hrs of sleep in a 32-hrs clinical protocol with standardized conditions [31], or, alternatively, a clinical or ambulant PSG performed for 32-hrs (night 1 + daytime + night 2) allowing ad libitum sleep showing > 19 hrs of sleep.

For level 2: not fulfilling criteria for level 1, but: 1. Actigraphy with sleep logs (2 weeks): strongly supports > 9 hours of sleep over 24 hrs on the majority of days, and 2. PSG (performed at end actigraphy recording): result 32-hrs protocol supports but does not meet the 19 hrs criterium, or a PSG for 32-hrs allowing ad libitum sleep is supportive but the PSG does not fully meet the 19 hrs criterium or is not performed as requested for level 1.

For both levels sleep efficiency for nocturnal sleep must be > 85% (at least when diagnostics are applied up to middle ages). If CSF hypocretin-1 measurement is performed, the hypocretin-1 concentration should be in the normal range.

These criteria are essentially expert opinion although particularly the 32 hours PSG protocol is supported by a study.

Severity criteria
See severity criteria of ENS paragraph 1.2.2. An existing and recently published scale might be useful [64].

Comorbidities
- Depression, anxiety, chronic fatigue, circadian disorders, attention disorders are relatively frequently seen
3.3 Diagnostic criteria for Idiopathic excessive sleepiness

The diagnosis can only be made after exclusion of sleep apnea, chronic sleep deprivation, and circadian disorders as likely causes of the sleep-related complaints (see ¶ paragraph 3.1). If the criteria for narcolepsy or IH are fulfilled, these diagnoses should be made.

Level 1

Definite*
1. EDS complaint (as defined earlier)*
2. Confirmed by PSG and MSLT: SL < 8 min**
3. Not fulfilling criteria for narcolepsy or IH

Level 2

Probable*:
1. EDS complaint (as defined earlier)*
2. MSLT: SL > 8 and < 12 min
3. Not fulfilling criteria for narcolepsy or IH

Subtype 1

“REM type“
1. ≥1 SOREM on PSG / MSLT
2. Findings on SART may be normal or abnormal

Subtype 2

“NREM type“
1. No SOREM on PSG / MSLT
2. Normal findings on SART

Subtype 3

”Attention type“
1. No SOREM on PSG / MSLT
2. Abnormal findings on SART
The complaint is present for at least three months.

** Those with inconsistent MSLT results over time will qualify for one of these categories, unless criteria for narcolepsy or IH are met.

*** The Sustained Attention to Response Task (SART) is a vigilance test to assess sustained attention. It has been applied and validated in patients suffering from hypersomnolence, ADHD and brain injury [7, 65, 66]. For the SART cut off values are defined: for the instruction “prefer accuracy over speed”, the cut-off is 6 [67]. The Psychomotor Vigilance Test (PVT) might be a good alternative for the SART but there are no cut-off data validated for patients with hypersomnolence [68].

**Severity criteria**
See severity criteria paragraph 1.2.1

**Comorbidities**
- Depression, anxiety, chronic fatigue, attention disorders are frequently seen.
Discussion

US clinicians were the first to create a classification of sleep and arousal disorders in 1979 [69]. In 1990 the first edition of the International Classification of Sleep Disorders (ICSD) was published, again with US physicians in the lead but representatives of sleep disorders associations outside the US became involved. The same holds true for the current edition of the classification, the ICSD3, published in 2014. All subsequent editions provided improvements but nevertheless it is not uncommon to be difficult or even impossible to make a proper diagnosis, including in people consulting us because of convincing complaints of hypsomnolence. In the absence of a proper diagnosis people who might deserve treatment may remain untreated. Discussions evoked by these experiences ultimately resulted in this position paper.

Clinicians, researchers, and particularly members of classification committees working in the field of hypsomnolence should acknowledge the lack of knowledge and understanding of the precise underlying neurobiological cause(s) of hypsomnolence and therefore the uncertainty if disorders we currently define are real disease entities. Moreover, the impact of lifestyle factors is often poorly characterised or appreciated. In such a situation a tendency to compensate the lack of knowledge by overemphasizing the qualities and properties of any biological markers we currently have should be resisted. It is our contention that the current classification system is unintentionally prone to this tendency. This is not only a problem for
patient care but may also prevent us from identifying additional biomarkers for sleep disorders.

We therefore suggest a different approach. Differences between the current and our approach:

- Our classification is much more complaint driven
- We emphasize that excessive daytime sleepiness is a multidimensional complaint and qualitatively different from an increased need for sleep.
- We use “hypersomnia” only to describe the presence of objectified ENS.
- We acknowledge that attentional problems frequently accompany disorders of hypsomnolence and isolated attention disorders should be separated from sleep disorders.
- Sleep deprivation, OSA and circadian disorders need to be initially excluded as primary causes of EDS. This allows the differentiation of true central disorders of hypsomnolence from disorders related to lifestyle disorders and sleep related breathing disorders. In case of doubt the effect of increased time in bed, a therapeutic test with CPAP, or circadian alignment must first be established. Guidelines from the National Sleep Foundation may help to identify the presence of sleep deprivation [70].
- We exclude possible confounders for changes in MSLT results over time.
- If MSLT results change over time we emphasise this should not necessarily have an immediate major impact on diagnostic categories and affect patients’ access to treatments, for example.
- Within our classification, patients can shift to more certain levels of diagnosis over time. This will potentially provide more insight in how disorders of hypsomnolence progress or develop and will help to guide future research agenda.
- We allow and formalise a certain level of diagnostic uncertainty, reflecting clinical reality in daily medical practice.
- There will be relatively few patients who will switch to a new diagnosis as a result of a new classification.

We realize that implementation of our proposal will have much impact on the current practices around the world. Different insurance systems and availability of the recommended tests (i.e., CSF orexin measurement, HLA typing, actigraphy, long term PSG recording) may be an issue for clinicians in some countries. However, our proposal is to move forward the field to improve the knowledge and management of patients affected with hypersomnolence. The main objectives are 1. to diagnose homogeneous groups of patients affected with these different hypersomnolence disorders, 2. to better understand the precise underlying neurobiological of such conditions (i.e., other than narcolepsy type 1), and finally 3. to improve the management of these patients. A registry to validate and optimize our suggested approach already exists in Europe within the European Narcolepsy Network (EU-NN) and could be extended to a global registry. In addition, studies to further validate the proposed diagnostic tools in a prospective setting should be initiated in several sleep labs around the world in the next few years. We also call for an international task force to formulate guidelines for the proper application of our suggested approach, The topics to be at least included:

- how to define, assess and treat chronic sleep deprivation in a practicable way
- what is the best and still feasible way to objectify ENS

For a better understanding of hypersomnolence disorders in general we must initiate studies to get insight in:

- what determines an individual’s sleep need and can we find biological markers to measure this need
- what is the relation between hypersomnolence and depression and how does it relate to the more studied close association between insomnia and depression
- what is the exact inter-relation between sleepiness, fatigue and disorders of attention

We are hopeful that further discussion will lead to a more consistent, widely accepted and workable future classification of central disorders of hypersomnolence. We also argue it will guide and prioritise our research agenda. Finally, we expect that more detailed attention to the multidimensional aspects of hypersomnolence complaints will facilitate and optimise clinical care tailored to individual patients.

**Conclusion**

We suggest the creation of a new consistent, complaint driven, hierarchical classification for central disorders of hypersomnolence; containing levels of certainty, and giving diagnostic tests, particularly the MSLT, a weighting based on its specificity and sensitivity in the diagnostic context.

We propose and define three diagnostic categories (with levels of certainty):

1. “Narcolepsy”
2. “Idiopathic hypersomnia”
3. “Idiopathic excessive sleepiness”

Except for narcolepsy, the diagnoses can only be made after excluding sleep apnea, sleep deprivation and circadian disorders as primary causes for hypersomnolence.
Practice Points

1. “Hypersomnolence” is the overarching name for the presence of EDS and/or ENS.

2. EDS and ENS are multidimensional and qualitatively different complaints.

3. There are large gaps in our understanding of the precise underlying neurobiological cause(s) of hypersomnolence and its associated disorders except for narcolepsy type 1. Moreover, the impact of lifestyle factors is often poorly characterised or appreciated.

4. Sleep deprivation, obstructive sleep apnea and circadian disorders need to be initially excluded as primary causes of hypersomnolence before considering a central disorder of hypersomnolence as cause of the complaint of excessive daytime sleepiness (except for narcolepsy with cataplexy / narcolepsy type 1).

5. For a reliable diagnosis of narcolepsy type 1, clear and detailed criteria for the presence of typical cataplexy are required.

6. The structure of a classification of sleep disorders, including the chapter on central disorders of hypersomnolence, must be complaint driven and not a mixture of complaint
driven diagnoses and diagnoses solely based on results of ancillary investigations (i.e. AHI, MSLT results).

7. We propose and define three diagnostic categories with different levels of certainty and subtypes: 1/ “Narcolepsy”; 2/ “Idiopathic hypersomnia”, and 3/ “Idiopathic excessive sleepiness”.

Research Agenda

We need to:

1. Understand what determines an individual’s sleep need and identify biological markers for it, as for disorders characterised by EDS and ENS.

2. Develop and validate a guideline to identify and treat chronic sleep deprivation as cause of excessive daytime sleepiness.

3. Better understand how disorders of hypersomnolence progress / develop over years.

4. Bridge the current gap between disorders of attention and disorders of hypersomnolence.

5. Better define and understand the proposed association between depression and hypersomnolence.

6. Better understand the inter-relation between sleepiness and fatigue.
References


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