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Clinical considerations for the diagnosis of idiopathic hypersomnia

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ABSTRACT

Idiopathic hypersomnia is a sleep disorder of neurologic origin characterized by excessive daytime sleepiness, with sleep inertia, long, unrefreshing naps, and prolonged nighttime sleep being key symptoms in many patients. Idiopathic hypersomnia is described in the *International Classification of Sleep Disorders*, 3rd Edition as a central disorder of hypersomnolence with distinct clinical features and diagnostic criteria; however, confirming the diagnosis of idiopathic hypersomnia is often challenging. Diagnosis of idiopathic hypersomnia is based on objective sleep testing and the presence of associated clinical features but may be difficult for clinicians to recognize and correctly diagnose because of its low prevalence, clinical heterogeneity, and symptoms, which are similar to those of other sleep disorders. The testing required for diagnosis of idiopathic hypersomnia also presents logistical barriers, and reliability of objective sleep measures is suboptimal. The pathophysiology of idiopathic hypersomnia remains unknown. In this review, clinical considerations related to the pathogenesis, diagnosis, and management of idiopathic hypersomnia will be discussed, including perspectives from the European Union and United States.

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1. Introduction

Hypersomnolence, including excessive daytime sleepiness (EDS) and excessive quantity of sleep (extended nocturnal sleep and long naps, collectively called hypersomnia), is a common complaint in the general population and negatively impacts everyday life [1]. EDS is distinct from fatigue (lack of energy or exhaustion, and difficulty sustaining activity levels), and refers to daily periods of irrepressible need to sleep or daytime lapses into sleep [2,3]. EDS and severe EDS are present in 15%–33% and 3.8%–11.8%, respectively, of the general population [1,4,5]. Risk factors for EDS include age, sleep deprivation, and medical conditions (eg, depression, anxiety, obesity, anemia, diabetes, and hypertension) [4,6]. EDS is a core diagnostic feature of idiopathic hypersomnia and a common symptom of many other disorders [2,7]. Subjective EDS can be measured using the Epworth sleepiness scale (ESS), a short, self-administered questionnaire for adults [8], and objective EDS can be measured using the multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT) [9].

Excessive quantity of sleep, also termed long sleep time (LST), occurs frequently in the general population, with approximately 8% of adults self-reporting ≥9 h in a typical 24-h period [10]. LST is related to sex and age, being more commonly reported by women and individuals ≤24 and ≥65 years of age [10]. The presence of long (>1 h), unrefreshing daytime naps is associated with long nighttime sleep [11]. Sleep duration can be captured using sleep diaries, wrist actigraphy, or polysomnography (PSG) in a laboratory setting [2].

Another feature sometimes associated with hypersomnolence disorders is sleep inertia (difficulty transitioning from sleep to wake), characterized by persistent sleepiness and poorly restorative sleep quality, frequent reentries into sleep, impaired performance, reduced vigilance, confusion, and irritability [2,12]. Sleep inertia is reported by 26% of healthy controls [13], but a severe form

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Abbreviations

AHI	apnea-hypopnea index
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
GABA	gamma-aminobutyric acid
ICSD	*International Classification of Sleep Disorders*
ICSD-2	*International Classification of Sleep Disorders*, 2nd Edition
ICSD-3	*International Classification of Sleep Disorders*, 3rd Edition
IHSS	idiopathic hypersomnia severity scale
ISS	insufficient sleep syndrome
LST	long sleep time
MSL,	mean sleep latency
MSLT	multiple sleep latency test
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OSA	obstructive sleep apnea
PLMS	periodic leg movements of sleep
PSG	polysomnography
SOREMP	sleep onset rapid eye movement period
TST	total sleep time

of sleep inertia, sometimes called "sleep drunkenness," does not occur in healthy controls [13]. Sleep inertia and other symptoms of hypersomnolence, including EDS and LST, can also be associated with sleep deprivation, delayed sleep phase, other sleep disorders (eg, obstructive sleep apnea [OSA]), medication or substance use/abuse, and psychiatric disorders (most typically depression) [2].

Idiopathic hypersomnia is a debilitating neurologic disorder of hypersomnolence with heterogeneous presentation. A recent claims analysis indicated a limited-duration prevalence estimate of 10.3 per 100,000 persons [14]. The primary symptom is EDS, with additional variable features of prolonged nighttime sleep, long (>1 h), unrefreshing naps, sleep inertia, and cognitive impairment [2,15]. Per the *International Classification of Sleep Disorders*, 3rd Edition (ICSD-3), EDS is present in all individuals with idiopathic hypersomnia [2], but appears to manifest differently than in narcolepsy type 1 (NT1); "sleep attacks" seem more specific to narcolepsy [16]. Patients with sleep inertia may depend on external sources (loud alarms; family members) to wake up in the morning, and even after exhausting these measures, may not awaken or may rapidly return to sleep, negatively impacting their work, school, and family life [15]. Sleep inertia is at least mild in 78%–100% of individuals with idiopathic hypersomnia [13,17–19], and severe (harder to awaken and greater tendency to return to sleep, with sluggishness, poor balance, and impaired reflexes [12]) in 36% [13], irrespective of sleep time [20]. After morning sleep inertia fades, individuals are usually able to remain awake throughout the day, but feel persistently drowsy, with brain fog (including memory and attention problems, frequently misplacing and forgetting things, and a feeling of one's mind "going blank" [7,13]) and renewed sleep inertia after naps. Prolonged sleep (≥11 h over a 24-h period, or ≥19 h over 32 h), as determined by objective sleep testing, is common [2,21]. Across studies, sleep duration ≥10 h has been reported in approximately 30%–50% of individuals with idiopathic hypersomnia, but could be present in up to approximately 70% in the authors' experience [2,19,22]. The prevalence of prolonged sleep may be underestimated since most sleep centers cannot perform extended PSG (>24 h) [15] and patients' responsibilities may prevent them from sleeping for the required duration; actigraphy monitoring remains underutilized.

Idiopathic hypersomnia was initially described in the early 1970s [23], and was included in the original *International Classification of Sleep Disorders* (ICSD; first published in 1990) as of its last iteration in 2001 [24]. In 2005, ICSD, 2nd Edition (ICSD-2) described two clinical phenotypes of idiopathic hypersomnia: with LST (≥10 h) and without LST (<10 h) [25]. However, the most recent 3rd Edition (ICSD-3, 2014) includes both phenotypes under one definition (mean sleep latency [MSL] ≤8 min or total sleep time [TST] ≥11 h), although research continues into whether these may be separate entities [11]. A 24-h TST ≥11 h is common but not mandatory for diagnosis [2].

In summary, idiopathic hypersomnia may be challenging for clinicians to recognize and diagnose because it is rare, clinically heterogeneous, and has symptoms that overlap with other disorders. Additionally, EDS is present in approximately one-third of the general population and can be comorbid with sleep apnea, depression, and other conditions, further complicating diagnosis [4]. This review will discuss clinical considerations related to the pathogenesis, diagnosis, and management of idiopathic hypersomnia, including perspectives from the European Union and United States.

2. Current idiopathic hypersomnia diagnostic criteria and considerations

2.1. Core features of idiopathic hypersomnia

Diagnosis of idiopathic hypersomnia involves careful clinical evaluation to exclude other disorders with similar symptoms, plus objective sleep testing (Fig. 1). Current ICSD-3 diagnostic criteria require the presence of EDS for ≥3 months, absence of cataplexy, and confirmatory objective sleep testing (Supplemental Table 1) [2,7], including MSL ≤8 min on MSLT and/or total 24-h TST of ≥660 min on PSG or wrist actigraphy (the latter also requiring a sleep log showing averaged 24-h TST ≥11 h daily over ≥7 days). In children and adolescents, normal sleep time for age should be considered when using 24-h TST to confirm diagnosis [2]. Age or sex do not significantly influence MSLT results (ie, sleep latency and number of SOREMPs) in a pediatric population [26]. The finding of two sleep onset rapid eye movement periods (SOREMPs) on MSLT (or less than one if nocturnal rapid eye movement [REM] latency was ≤15 min) is currently an exclusion criterion. An ESS score that is not persistently high may suggest a different disorder.

The SOREMP requirement for diagnosis remains controversial in the case of patients with MSL >8 min on MSLT but with confirmed sleep duration ≥660 min on a 24-h PSG. A patient with ≥2 SOREMPs, MSL >8 min, and 24-h TST ≥660 min should be considered for a diagnosis of idiopathic hypersomnia, despite not meeting ICSD-3 criteria for either narcolepsy or idiopathic hypersomnia. Recommending sleep extension prior to scheduling diagnostic testing may be helpful to exclude normal long sleep, because long sleepers will generally note resolution of EDS symptoms and feel fully refreshed upon awakening when they meet their individual sleep need. Because of frequently normal MSLT findings in idiopathic hypersomnia with LST [20,22] and low MSLT test-retest reliability [27], researchers have proposed objective evidence of LST as a more reliable endpoint [3]. However, 2014 ICSD-3 criteria

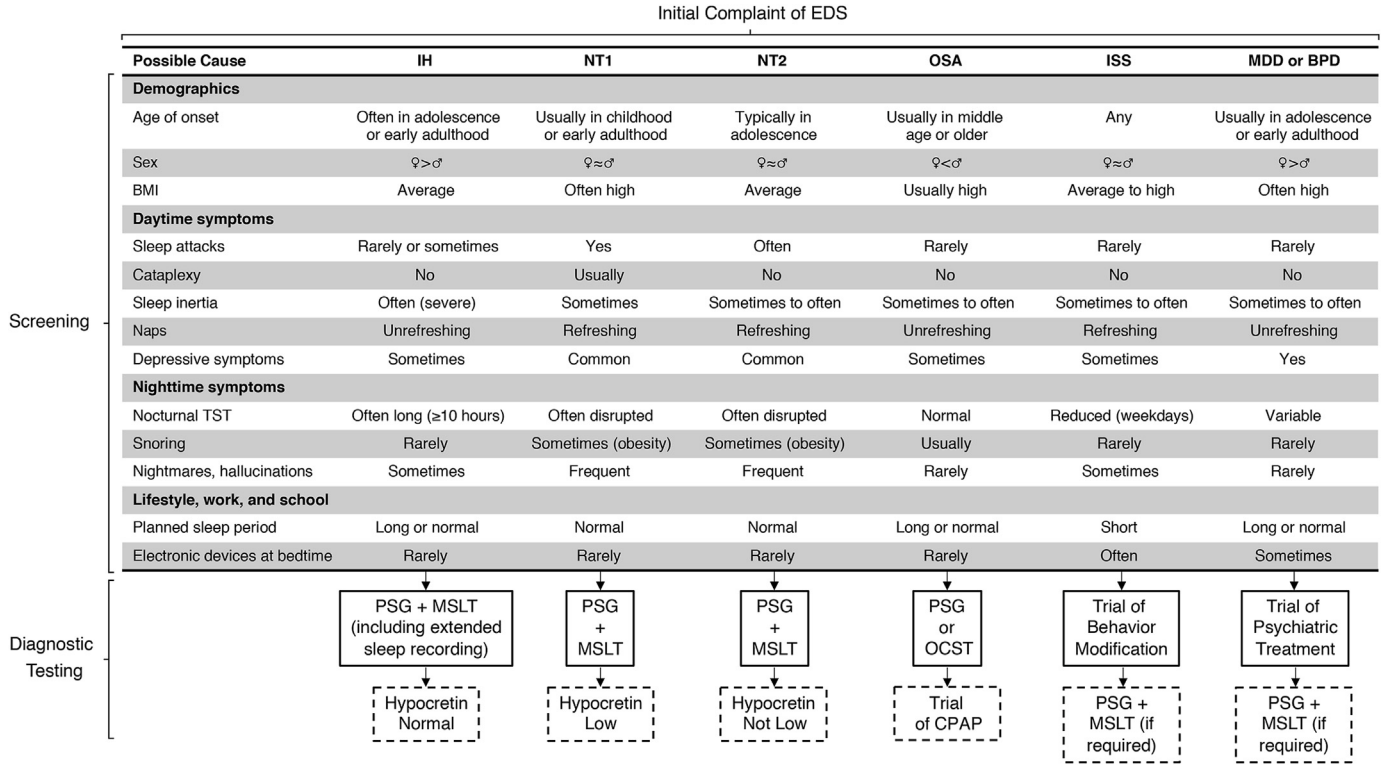

Fig. 1. An Initial Approach to Diagnosis of Idiopathic Hypersomnia or Other Sleep Disorders in Individuals Presenting With a Complaint of EDS
Dashed boxes indicate follow-up diagnostic testing.
BMI, body mass index; BPD, bipolar disorder; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; IH, idiopathic hypersomnia; ISS, insufficient sleep syndrome; MDD, major depressive disorder; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OCST, out-of-center sleep testing; OSA, obstructive sleep apnea; PSG, polysomnography; TST, total sleep time.

remain the standard for diagnosis, with contemporary modifications proposed in 2020 [3], including stricter criteria and use of extended-duration objective sleep testing involving in-laboratory PSG or outpatient prolonged PSG and/or electroencephalography testing protocols [21,28].

2.2. Ancillary features of idiopathic hypersomnia

Per ICSD-3 criteria, sleep inertia is not required for diagnosing idiopathic hypersomnia, but is an important, common symptom that clinicians should recognize and quantify [2]. Sleep inertia can be measured using several instruments, including the sleep inertia questionnaire (which has been validated only in individuals with depression) [29], the hypersomnia severity index (a nine-item tool to measure hypersomnia severity, distress, and impairment, which has been validated in patients with sleep disorders) [30], the psychomotor vigilance task (PVT; a short and simple tool to measure behavioral alertness and sustained attention, which correlates with symptoms of sleep inertia in patients with central hypersomnolence disorders) [31,32], and the idiopathic hypersomnia severity scale (IHSS; a 14-item, patient-reported, validated questionnaire assessing idiopathic hypersomnia symptoms' frequency, duration, and impacts, which has demonstrated specificity and reliability in detecting significant changes following treatment) [33,34]. The severity of sleep inertia in idiopathic hypersomnia, assessed with the IHSS, correlates with impairment of PVT performance [31]. However, PVT results do not discriminate among disorders with severe sleep inertia [31], and none of these questionnaires have yet been used as a screening tool in clinical practice.

Patients frequently report automatic behaviors upon waking and when drowsy during the day, whereas hypnagogic hallucinations and sleep paralysis are less frequent [13,20,22]. These latter symptoms are not uncommon in the general population; the prevalence of hallucinations has been estimated as 6.6% (hypnopompic) to 24.8% (hypnagogic), and the prevalence of sleep paralysis as 7.6% [35,36]. Nightmares in idiopathic hypersomnia are rare, and half of patients report frequent "blackout" of their nights upon awakening, whereas around 20% complain of "dreaming too much" [37]. Although there is no definition of "good" sleep in idiopathic hypersomnia (in contrast with disrupted sleep in other disorders), other than the supportive finding of sleep efficiency ≥90% [2], one may expect that criteria for other disorders would be absent in people with idiopathic hypersomnia (eg, apnea-hypopnea index [AHI] <5, and periodic leg movements of sleep [PLMS] <15/hour). Some patients with idiopathic hypersomnia may have variable sleep-wake patterns due to their long naps and nocturnal sleep (when feasible); therefore, it is always important to stabilize bedtimes and wake times with an appropriate duration of time in bed prior to establishing the diagnosis.

3. Diagnostic challenges in idiopathic hypersomnia

Objective sleep testing required for diagnosing idiopathic hypersomnia presents many challenges. Despite the inclusion of sleep test results in ICSD-3 diagnostic criteria, prolonged PSG recordings are less likely to be performed in the United States than in Europe due to expense and reimbursement issues, sometimes preventing complete diagnostic evaluation.

The MSLT has poor test-retest reliability in clinical populations with central nervous system hypersomnolence disorders [27,38,39], especially idiopathic hypersomnia, because of MSL variability and number of SOREMPs across testing sessions. In a retrospective study, 25% of patients meeting MSLT criteria initially met criteria again during a second test [27]. In another retrospective study, >30% of patients crossed the threshold of ≥2 SOREMPs between sleep studies, changing from a diagnosis of idiopathic hypersomnia (based on initial MSLT findings) to narcolepsy type 2 (NT2; based on the second MSLT) [38]. Low test-retest reliability could be explained by intrinsic features of the MSLT or by spontaneous fluctuations in symptom severity in idiopathic hypersomnia and NT2, implying that there may be substantial phenotypic overlap between these categories. These findings challenge the validity of the required 8-min MSL cutoff or TST ≥11 h and reinforce a possibility for reassessment in patients with a clinical presentation suggestive of idiopathic hypersomnia who do not fulfill ICSD-3 diagnostic criteria. Patients with idiopathic hypersomnia whose hypersomnolence resolved or improved during long-term treatment with wake-promoting medications should be reassessed under drug-free conditions, as the disorder may improve or spontaneously remit in approximately 14%–26% of cases [40,41]. Consideration of MSLT parameters besides MSL and number of SOREMPs has been proposed for differential diagnosis of central hypersomnolence disorders, including sustained sleep latency, REM sleep latency, time spent in REM sleep, and sleep stage sequence [42–44].

The PSG also has limitations, and efforts are underway to develop more precise and specific diagnostic criteria based on this tool [15]. Extended-duration PSG protocols have been proposed for confirming idiopathic hypersomnia, as long sleep may be a more reliable symptom than propensity to fall asleep during the day [15,20,21,45]. The current ICSD-3 diagnostic criteria call for ≥660 min of sleep in a 24-h period on PSG based on one study [20], or wrist actigraphy in association with a sleep log, but do not otherwise specify details of the protocol (eg, setting) nor account for factors expected to impact total sleep duration (eg, age) [2]. That 48-h protocol includes an overnight PSG, then daytime MSLT, then a second PSG of 18–20 h comprising overnight sleep and uninterrupted naps; this protocol has normative data on long-term sleep monitoring [15,20]. Another standardized protocol includes PSG and modified MSLT, then a 32-h bed rest recording (one night, one day, one night) [15,21] with normative data reported. A 60-h protocol includes PSG recording for 48 h, then an MSLT [15,45]. These extended-duration protocols could be performed in any region, but are not uniformly available or used outside their originating groups; they are only performed regularly in select European Union countries. Both extended-duration PSG and actigraphy have limitations for measuring extended sleep duration in idiopathic hypersomnia [15,46]. There are few standard protocols (ie, sleep time, time in bed, possible activity, light, etc) or normative measures (ie, with good specificity and sensitivity) for extended-duration PSG, as outlined in the protocols above. Extended-duration actigraphy has not been validated in idiopathic hypersomnia versus healthy controls. Additionally, optimal actigraphic settings have not been established, and the procedure is not typically reimbursed by insurance in the United States and European Union. For both extended-length procedures, there is increased cost and inconsistent availability. Further study of extended-length protocols, which allow for quantification of excessive sleep duration to diagnose idiopathic hypersomnia with LST, is needed. However, it is still unclear whether recording excessive sleep duration can aid in formally discriminating among the diagnoses of NT2, idiopathic hypersomnia with LST, and physiological long sleep [3]. Also, as LST is not currently a requirement for diagnosis of idiopathic hypersomnia, and a subset of patients does not exhibit the LST phenotype [2], extended monitoring procedures are unlikely to become the only method of diagnosing idiopathic hypersomnia unless the criteria regarding long sleep are modified. New tools and technologies must be developed to record sleep while individuals are in their daily living environments, with analysis possibly aided by artificial intelligence. Moreover, the absence of any pathognomonic clinical features or known biomarkers further hinders the diagnosis of idiopathic hypersomnia [16].

Idiopathic hypersomnia, as currently defined, remains a diagnosis of exclusion [47]. A challenge is in not only discriminating idiopathic hypersomnia from other disorders of hypersomnolence, but in establishing whether symptoms or test results are due to neurologic, psychiatric, or other medical causes [47]. EDS is a symptom of several sleep disorders that must be considered in the differential diagnosis of idiopathic hypersomnia [2,7,48], such as OSA, narcolepsy, insufficient sleep syndrome (ISS; especially in normal long sleep), and circadian phase delay. Also, non-REM parasomnias, which can cause EDS [49–51], may be comorbid, albeit rarely, in idiopathic hypersomnia [52]. Other diagnoses must be considered, as well as head injury and obesity. EDS can persist in OSA despite adherence to continuous positive airway pressure (CPAP) therapy [53,54]. Furthermore, even in the absence of OSA, obesity can be associated with EDS and LST, which appears to be related to a metabolic and/or circadian abnormality [55,56].

Therefore, to accurately diagnose idiopathic hypersomnia, one must consider the overall picture, beyond just ICSD-3 criteria. The individual patient's characteristics, signs, and symptoms must be elicited and synthesized to inform an appropriate, efficient approach to diagnostic testing (Fig. 1). A diagnostic algorithm based on standard practice in France is available in the literature [47]; however, national and international variations in practice (eg, with regard to adoption of prolonged PSG testing) preclude development of a universal algorithm.

3.1. Idiopathic hypersomnia versus narcolepsy

NT1 and NT2 have the same MSL diagnostic criterion as idiopathic hypersomnia (≤8 min) but require two or more SOREMPs, as opposed to fewer than two SOREMPs [2] (Figs. 1 and 2). The presence of cataplexy or low cerebrospinal fluid (CSF) levels of hypocretin-1 clearly differentiates NT1 [2]. Distinguishing idiopathic hypersomnia from NT2 is more challenging, as these disorders may differ only by the presence of REM sleep during MSLT naps (ie, number of SOREMPs) [2]. Sleep inertia is more common and often more severe in idiopathic hypersomnia compared with NT2 (Figs. 1 and 2) [15,19]. The severity of sleepiness in idiopathic hypersomnia did not differ from that in narcolepsy (mean ESS scores ranged from 14.1 to 17.9 in idiopathic hypersomnia, 14.5 to 16.7 in NT2, and 16.6 to 18.5 in NT1 [17,18,33,57,58]). However, people with idiopathic hypersomnia tend to feel sleepy all day, and are unrefreshed after long naps, but are generally able to remain awake, whereas people with narcolepsy may feel temporarily refreshed after short naps with dream content, and sometimes experience episodes of severe, irresistible sleepiness (“sleep attacks”) [2,17,18,57,58]. Abnormal REM sleep phenomena such as frequent vivid dreams, sleep paralysis, and hypnagogic hallucinations are more frequent in narcolepsy [52] (Fig. 2).

In contrast to narcolepsy, the frequency of the HLA DQB1*0602 haplotype in idiopathic hypersomnia is similar to the general population [40]. Carrier frequency of the HLA DQB1*0602 haplotype ranges from 18%– 31% in idiopathic hypersomnia, 95%–98% in narcolepsy with cataplexy, 26%–100% in narcolepsy without cataplexy and normal CSF hypocretin levels, and 15%–40% in controls (40.2% in African American controls) [20,40,59–61].

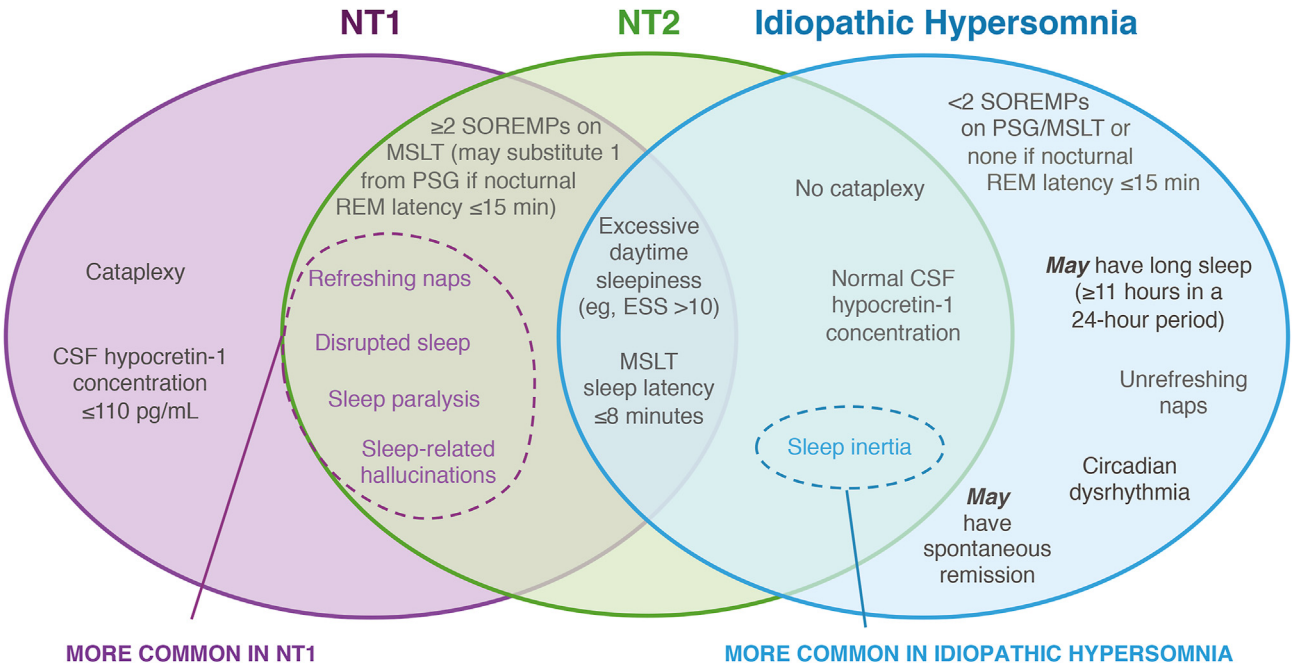

Fig. 2. Diagnostic Features of NT1, NT2, and Idiopathic Hypersomnia [2,12,27,105,106]
CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography; REM, rapid eye movement; SOREMP, sleep onset rapid eye movement period.

3.2. Idiopathic hypersomnia versus OSA

In contrast with idiopathic hypersomnia (Fig. 1), OSA is often diagnosed in middle-aged or older men with higher body mass indices [2,20,40,62]. Similar to idiopathic hypersomnia, patients with OSA lack cataplexy; however, they have normal nighttime sleep durations and excessive snoring [2,18]. Patients with idiopathic hypersomnia often have severe sleep inertia, whereas patients with OSA typically do not [2,19,32]. Diagnostic testing for OSA may begin with testing (PSG or out-of-center sleep testing); if positive, that may be followed by a trial of CPAP if desired [2].

3.3. Idiopathic hypersomnia versus ISS

In ISS, TST is shorter than expected for age due to intentional curtailment (typically during the week), and EDS resolves with extension of sleep time [2,63]. ISS can occur at any age and is approximately equally prevalent in males and females (Fig. 1) [2]. ISS is similar to idiopathic hypersomnia in that patients may experience some sleep inertia, depressive symptoms, and hallucinations; however, symptoms in ISS result from suboptimal sleep [2,18,63], whereas in idiopathic hypersomnia, symptoms do not resolve with additional sleep [2,64].

3.4. Idiopathic hypersomnia versus mood disorders

Claims analyses support the presence of comorbid conditions that share symptoms with idiopathic hypersomnia, which may confound diagnosis [65]. Consistent with clinical experience described earlier, common comorbidities in adults with newly diagnosed idiopathic hypersomnia include mood disorders (32.1%), depressive disorders (31.0%), and anxiety disorders (30.7%). Sleep apnea and mood disorders should be treated before diagnosing idiopathic hypersomnia.

Hypersomnia in mood disorders, especially depression, can present as sleepiness with difficulty getting out of bed in the morning [64]. However, sleep inertia may be more severe in people with idiopathic hypersomnia, who more frequently require assistance from another person to awaken [64]. Some patients with depression may desire to remain in bed and overestimate their sleep duration because they include time in bed when estimating sleep time [28] (Fig. 1). In depression, both EDS and LST can be present [66]. In the authors' experience, the sleepiness and sleep inertia of depression are more marked in the morning (which is also true in idiopathic hypersomnia) and, importantly, often congruent with low mood, which improves in the late afternoon. LST may persist during euthymic periods [67]. Symptoms of depressed mood are common in patients with idiopathic hypersomnia [20,57]; however, although subjective sleepiness has been associated with increased odds of depressive symptoms, objective sleepiness on the MSLT has been associated with decreased odds of depressive symptoms [68], and medications may confound the validity of objective sleep testing [69–71] (Fig. 1). TST and sleep efficiency are greater, and MSL on the MSLT is shorter, in people with idiopathic hypersomnia compared with hypersomnia associated with a psychiatric disorder [64]. MSL is usually >8 min with mood disorders or hypersomnia associated with a psychiatric disorder [72]. For clinical reasons, it may not be possible to discontinue antidepressants prior to sleep testing, in which case the clinician must determine whether information from an MSLT performed during antidepressant treatment is helpful in the diagnosis.

3.5. Iatrogenic hypersomnolence

Medication/Substance use/abuse complicates differential diagnosis. Drug-induced hypersomnolence can occur due to sedatives, hypnotics, and other medications that cause sedation incidentally [73], including antidepressants, H1 antihistamines, antipsychotics, and hypocretin antagonists. Stimulant withdrawal can also result in

hypersomnolence. A careful clinical history is usually sufficient to unveil medication or substance use/abuse, but depending on the clinical setting, we may recommend a urine drug screen at the time of objective sleep testing to exclude confounding substances.

4. Pathogenesis

The pathophysiology of idiopathic hypersomnia remains unknown. No consistent abnormalities in the key wakefulness-promoting or sleep-wake circuit neurotransmitters have been found [2], with normal levels of CSF hypocretin-1, histamine, and tele-methylhistamine [74–77], albeit with some inconsistencies [59,78]. A recent study found no striking differences in CSF biogenic amines, their metabolites, or trace amine levels in participants with idiopathic hypersomnia, NT1, or NT2 and individuals without objective EDS [79]. Interestingly, the presence of an endogenous gamma-aminobutyric acid (GABA)-like substance in the CSF of individuals with idiopathic hypersomnia (and other stimulant-resistant disorders of hypersomnolence) that modulates GABA-mediated inhibitory effects on arousal [80,81] has been reported, but not replicated [82]. Another proposed contributor to idiopathic hypersomnia is circadian mechanisms (eg, longer circadian period or long biological night) [20,83–86]. The frequent family history of idiopathic hypersomnia symptoms suggests genetic predisposition [7,87], but no specific genetic locus or inheritance pattern has been demonstrated. Family history of excessive sleepiness, idiopathic hypersomnia, or another disorder of hypersomnolence is seen in 34%–37% of patients with idiopathic hypersomnia [40,41,62].

Neuroimaging suggests that persistent sleepiness in idiopathic hypersomnia may relate to abnormal neural activity in an arousal system and intrusion of a sleep-like state during wakefulness [15]. The first positron emission tomography study in participants with NT1 and idiopathic hypersomnia showed hypermetabolism in the anterior and middle cingulate and insula in the resting wake state, compared with controls, which was hypothesized to represent an altered arousal system [88]. Brain scintigraphy in participants with idiopathic hypersomnia showed regional cerebral blood flow decreases in the medial prefrontal cortex and posterior cingulate cortex, and increases in the amygdala and temporo-occipital cortices, during resting wakefulness; this pattern is similar to regional cerebral blood flow during non-REM sleep, potentially consistent with incomplete transitions between sleep-wake states [89]. Hypermetabolism in the precuneus and inferior parietal lobule was observed in participants with NT1 and idiopathic hypersomnia compared with controls, although regional patterns of hypermetabolism differed between the groups [90].

Classical PSG findings in idiopathic hypersomnia with LST demonstrate normal architecture, with prolonged, high sleep efficiency that may include one to several additional sleep cycles [20,28]. However, there have been reports of other heterogeneous PSG abnormalities [91–93], decreased percentage of slow-wave sleep [91], increased REM sleep [91], and altered sleep quality and stability [92], likely due to differing diagnostic criteria across studies.

The heterogeneous nature of symptoms belonging to currently broadly defined idiopathic hypersomnia suggests the possibility of different etiologies [3,47]. There appear to be separate phenotypes for individuals requiring increased sleep duration compared with a normal amount of sleep [3]. A cluster analysis including nighttime and daytime symptoms, nocturnal PSG, and MSLT in 96 patients with central hypersomnolence disorders differentiated three main clusters, including NT1, NT2 and idiopathic hypersomnia without LST, and idiopathic hypersomnia with LST, suggesting that this last category has a homogeneous phenotype [22]. Distinguishing these phenotypes will likely require novel discoveries providing better insight into the underlying neurobiology and pathophysiology [2].

5. Treatment

In the United States, lower-sodium oxybate (LXB; Xywav®) has been approved to treat idiopathic hypersomnia in adults since August 2021 [94]. In a phase 3, placebo-controlled, double-blind, randomized withdrawal study in adults with idiopathic hypersomnia, LXB demonstrated statistically significant, clinically meaningful effects on EDS, idiopathic hypersomnia symptom severity, and self-reported patient global impression of change [95]. This study marked the first use of the IHSS in a clinical trial of an idiopathic hypersomnia treatment [95]. LXB is approved for use in adults with idiopathic hypersomnia [94]; no treatments are approved for use in pediatric patients, and no clinical studies of pediatric idiopathic hypersomnia have been performed. LXB is not approved for the treatment of idiopathic hypersomnia outside of the United States.

Treatments typically used off-label for treating idiopathic hypersomnia include alerting agents (wake-promoting agents or stimulants), despite limited evidence for efficacy in this population [96]. Modafinil was previously approved in Europe to treat idiopathic hypersomnia, although this indication was rescinded in 2010 [97]. Pharmacotherapy reportedly controls EDS satisfactorily in approximately 65%–72% of patients; modafinil, methylphenidate, and dextroamphetamine monotherapy are frequently used, while high-dose monotherapy or combination polytherapy may be necessary in up to one-third of patients [40,41,62]. Few randomized, placebo-controlled trials have been conducted in idiopathic hypersomnia; most data are from observational studies and case series [96]. However, randomized, double-blind, placebo-controlled clinical trials showed that modafinil was an effective treatment for EDS in participants with idiopathic hypersomnia without LST [97,98]. Other medications, including clarithromycin [99,100], flumazenil [81], and pitolisant [81,101], have shown some effect on EDS in participants with hypersomnolence. A $GABA_B$ receptor agonist, baclofen, has also been reported as a potential treatment [19].

6. Discussion and expert opinion

Distinguishing EDS with its various causes from idiopathic hypersomnia is challenging. In the absence of pathognomonic features, suspicion for idiopathic hypersomnia can be raised by characteristic, albeit nonspecific features (Fig. 1), including early-life onset of symptoms and female sex [2]. This contrasts with the typically older, predominantly male OSA population [2]. Assessment of qualitative daytime hypersomnolence symptoms may provide additional clues. For example, severe sleep inertia and long, unrefreshing naps are characteristic of idiopathic hypersomnia and suggest that NT1 is unlikely, whereas clear cataplexy establishes an NT1 diagnosis and excludes idiopathic hypersomnia [2]. Extended nocturnal sleep duration suggests idiopathic hypersomnia, but is not observed in idiopathic hypersomnia without LST, and is found in the general population as an isolated finding without daytime somnolence (ie, long sleepers [typically defined as adults sleeping $\geq$10 h/night or children sleeping >2 h more than normal for age]) [2]. Sleep extension during weekends or other periods, suggesting unfulfilled sleep need, may represent a clinical biomarker of

idiopathic hypersomnia after exclusion of ISS [28,102]. It has been found that patients with idiopathic hypersomnia sleep an average of 3 h longer on weekends and holidays than during the week [13], and many patients extended their sleep duration and time in bed during the COVID-19 pandemic and associated lockdown [103,104].

Due to high sleep efficiency and generally normal REM sleep physiology in idiopathic hypersomnia, nighttime symptoms (eg, sleep paralysis, hypnogogic/hypnopompic hallucinations) are rare. Although nonspecific, these symptoms, if frequent and intensive, can help differentiate idiopathic hypersomnia and narcolepsy [52]. Nightmares are not more frequent than in the general population, and REM sleep behavior disorder is not comorbid to idiopathic hypersomnia, unlike narcolepsy [52]. Other nocturnal sleep characteristics may be difficult to elicit because patients frequently lack insight into their sleep behaviors. Therefore, history from a sleep companion, caregiver, or parent regarding disruptive snoring, breathing pauses, or parasomnia behaviors may inform diagnostic considerations. Disruptive snoring is most frequent in OSA, yet snoring and obesity can be comorbid in patients with narcolepsy but rarely in idiopathic hypersomnia [2,95]. Disrupted nighttime sleep is common in NT1 and uncommon in idiopathic hypersomnia [92].

Environmental influences are other components of screening for idiopathic hypersomnia. Inadequate sleep must be corrected before the evaluation continues, ensuring patients allocate enough time for sleep and that their sleep is not disrupted by using electronic devices in bed, or other environmental factors (eg, noisy or hot bedroom) that could reduce sleep quality or quantity. ISS can be difficult to exclude, and a careful history of the daily sleep pattern, including weekend sleep, should be taken, ideally using sleep logs or actigraphy. A trial of extended sleep duration should be undertaken if ISS is suspected. We recommend the patient keep a sleep log for about a month, and after a 2-week baseline, extend their sleep by 1–2 h for 2 weeks while logging their level of daytime sleepiness with the ESS. If sleepiness does not improve, we then test for other causes of sleepiness using PSG and MSLT, ideally with confirmatory actigraphy to ensure accurate estimation of sleep duration prior to laboratory testing [2]. Use of sedating substances (eg, medications, alcohol) is another potential source of EDS to consider.

In most patients presenting with hypersomnolence, narrowing diagnostic possibilities to a single disorder after screening, history, and physical examination is difficult, except when there is unambiguous cataplexy. In the authors' experience, symptoms of idiopathic hypersomnia vary across time within an individual patient's disease course. Thus, screening should weigh which disorders are most likely so that the subsequent workup (diagnostic testing) can rapidly lead to a clear diagnosis (Fig. 1). Although EDS is currently required in diagnostic criteria, EDS may appear to be absent in patients with idiopathic hypersomnia with LST in clinical practice (although this is rare) because long sleep duration may offset any potential EDS. However, in most cases, patients with idiopathic hypersomnia complain of EDS, drowsiness, fatigue, and sleep inertia, regardless of their TST. Total 24-h sleep time $\geq$660 min is included among diagnostic criteria (though not required for diagnosis, if mean sleep latency on MSLT is $\leq$8 min [2]), but extended PSG [20] is not feasible for all patients (eg, due to reimbursement issues). However, in these and other cases, idiopathic hypersomnia can still be identified and distinguished from normal long sleep by the presence of other characteristic symptoms, such as sleep inertia [2]. Furthermore, ESS scores do not differentiate among idiopathic hypersomnia, NT1, and NT2 [17,18,33,57,58]. Updated ICSD-3 criteria are needed, as recently proposed by a consensus of European experts, to emphasize a new criterion: excessive quantity of sleep, which usually cannot be accommodated because of work and other responsibilities [3].

Testing for idiopathic hypersomnia begins with PSG and MSLT, often with preceding actigraphy monitoring and/or sleep diary to document adequate sleep and time in bed. Preparation before sleep testing and careful attention to protocol are important for reliable results, including counseling on adequate time in bed, as is tapering of antidepressants and other confounding sedating and/or REM sleep suppressant medications in advance whenever feasible and safe. For example, if the sleep period is truncated after 8 h for a long sleeper patient, or even at the 6-h mark, the resulting sleepiness can affect the MSLT. Possibly reflecting differences in sleep duration as part of sleep testing, one study showed that 71% of patients with idiopathic hypersomnia with LST had MSL >8 min [20], and other studies showed that some patients had MSL of 4–10 min [21,22]. Repetition of sleep testing is expensive and inconvenient.

Idiopathic hypersomnia may coexist with other disorders, such as depression, but is incompatible with others, such as narcolepsy. If doubt remains following initial tests, CSF hypocretin levels can rule out NT1 in those with demonstrated genetic predisposition (ie, HLA DQB1*0602 positivity; however, a caveat is that DQB1*0602 positivity alone is nonspecific and insufficient for NT1 diagnosis, given its relatively high prevalence in the general population [2]). An iterative approach employing other tests or trials of therapy (eg, treatment with CPAP or other measures to address sleep-disordered breathing) may be necessary to identify and address confounding comorbid conditions. Current diagnostic criteria for idiopathic hypersomnia are controversial; thus, the search for additional biomarkers and debate about borders between sleep disorders must continue.

In summary, the well-informed healthcare practitioner is equipped to distinguish idiopathic hypersomnia from other conditions marked by EDS and other overlapping symptoms through thoughtful application of both clinical judgment and appropriate testing, thus enabling patients to receive the most effective treatment for this debilitating sleep disorder.

7. Practice points

1. Idiopathic hypersomnia is a sleep disorder of unknown etiology and low prevalence characterized by excessive daytime sleepiness, with or without long sleep duration, unrefreshing naps, and sleep inertia.
2. Demographic (eg, higher female prevalence) and symptomatic features of the idiopathic hypersomnia population form a typical profile, but with high heterogeneity and substantial overlap with other sleep disorders.
3. Careful clinical history, with consideration of associated comorbidities and documentation of sleep patterns over at least 2 weeks, is important before considering sleep testing.
4. Efficient screening and workup are important to reduce diagnostic delay so that patients may receive timely, effective therapy.
5. The United States Food and Drug Administration approved lower-sodium oxybate in 2021 for the treatment of idiopathic hypersomnia in adults.

8. Research agenda

1. More research is needed into protocols for diagnostic testing to improve accuracy, reliability, and convenience, especially approaches for in-laboratory and in-home recordings for extended sleep duration.

2. The degree of distinction and possible overlap between idiopathic hypersomnia and narcolepsy type 2, both in terms of pathophysiology and diagnostic features, should be further examined.
3. Better understanding of idiopathic hypersomnia as a disease state would lead to the identification of reliable biomarkers and inform rational treatment strategies.
4. The IHSS should be considered for disease characterization.

Declaration of competing interest

Y Dauvilliers is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Avadel, Harmony Biosciences, Idorsia, Orexia, Takeda, Paladin, and Bioprojet. RK Bogan is a shareholder of Watermark Medical and Healthy Humming, LLC; serves on the board of directors for Watermark; is a medical consultant to Jazz Pharmaceuticals, Harmony Biosciences, Avadel Pharmaceuticals, Takeda, and Oventus; has conducted industry-funded research for Avadel, Axsome, Bresotec, Bayer, Idorsia, Suven, Jazz, Balance, NLS, Vanda, Merck, Eisai, Philips, Fresca, Takeda, LivaNova, Roche, Sanofi, Sommetrics, and Noctrix; and is on the speakers bureau for Jazz, Eisai, and Harmony. I Arnulf has participated in advisory boards for UCB Pharm, Idorsia, Ono Pharma, and Roche Pharma. TE Scammell has consulted for Avadel, Axsome, Consynance, Eisai, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Merck, Orion Pharma, Takeda, and Tris Pharmaceuticals and has received research grants from the National Institutes of Health, Merck, Jazz, and Takeda. EK St Louis receives research support from the National Institutes of Health, the National Institute of Neurological Disease and Stroke, the National Institute on Aging, and the National Heart, Lung, and Blood Institute. MJ Thorpy has received research/grant support and consultancy fees from Jazz Pharmaceuticals, Harmony Biosciences, Balance Therapeutics, Axsome Therapeutics, and Avadel Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2022.101709.

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