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Central Disorders of Hypersomnolence
Focus on the Narcolepsies and Idiopathic Hypersomnia

Zeeshan Khan, DO; and Lynn Marie Trotti, MD

The central disorders of hypersomnolence are characterized by severe daytime sleepiness, which is present despite normal quality and timing of nocturnal sleep. Recent reclassification distinguishes three main subtypes: narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia (IH), which are the focus of this review. Narcolepsy type 1 results from loss of hypothalamic hypocretin neurons, while the pathophysiology underlying narcolepsy type 2 and IH remains to be fully elucidated. Treatment of all three disorders focuses on the management of sleepiness, with additional treatment of cataplexy in those patients with narcolepsy type 1. Sleepiness can be treated with modafinil/armodafinil or sympathomimetic CNS stimulants, which have been shown to be beneficial in randomized controlled trials of narcolepsy and, quite recently, IH. In those patients with narcolepsy type 1, sodium oxybate is effective for the treatment of both sleepiness and cataplexy. Despite these treatments, there remains a subset of hypersomnolent patients with persistent sleepiness, in whom alternate therapies are needed. Emerging treatments for sleepiness include histamine H3 antagonists (eg, pitolisant) and possibly negative allosteric modulators of the gamma-aminobutyric acid-A receptor (eg, clarithromycin and flumazenil). CHEST 2015; 148(1):262-273

ABBREVIATIONS: AASM = American Academy of Sleep Medicine; CSF = cerebrospinal fluid; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; FDA = US Food and Drug Administration; GABA = gamma-aminobutyric acid; HLA = human leukocyte antigen; ICSD-3 = *International Classification of Sleep Disorders, Third Edition*; IH = idiopathic hypersomnia; MSL = mean sleep latency; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; PSG = polysomnography; RCT = randomized controlled trial; REM = rapid eye movement; SOREMP = sleep-onset rapid eye movement period; SSRI = selective serotonin reuptake inhibitor

Sleepiness is a common experience, with the prevalence of excessive daytime sleepiness (EDS) occurring at least 3 d/wk ranging from 4% to 21%.[1] Such sleepiness may be caused by medical conditions, sleep disorders, illicit and prescribed substances, work and family demands (including shift work), and insufficient sleep time. Insufficient sleep is a particularly common cause of EDS, as more than one-third of Americans are sleep deprived.[2]

This review focuses on the central disorders of hypersomnolence, a group of sleep disorders characterized by EDS in the absence of disrupted nocturnal sleep or circadian rhythm disorders. The first of these disorders to be comprehensively described was narcolepsy, dating back to a

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AFFILIATIONS: From the Emory Sleep Center, Emory University School of Medicine, Atlanta, GA.

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CORRESPONDENCE TO: Lynn Marie Trotti, MD, 12 Executive Park Dr NE, Atlanta, GA 30329; e-mail: Lbecke2@emory.edu

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case published in 1880 by Jean Baptiste Gélineau of a 38-year-old wine merchant with > 200 sleep attacks per day.[3] Idiopathic hypersomnia (IH) was then detailed by Bedrich Roth in a series of 642 patients seen over 30 years.[4] The classification, diagnosis, and treatment of the central disorders of hypersomnolence have evolved considerably since these early descriptions and will be the focus of this review. Together, these hypersomnolence disorders account for substantial morbidity and impairments in quality of life.[5-9]

Clinical Features, Diagnosis, and Classification

EDS is the cardinal feature of the central disorders of hypersomnolence. It is defined as the "inability to stay awake and alert during major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep."[10] It can be confused with fatigue, but while fatigue presents with a lack of energy without inadvertent or excessive sleep, sleepiness implies an increased propensity to sleep. The most recent version of the *International Classification of Sleep Disorders, Third Edition* (ICSD-3) subdivides the central disorders of hypersomnolence into eight categories (Table 1).[10] While insufficient sleep syndrome (ie, sleepiness caused by short sleep times and cured by sleep extension) is categorized as one of the eight hypersomnolence syndromes, insufficient sleep time must be excluded for the other diagnoses. This can be accomplished using patient-completed sleep logs or actigraphic monitoring over a 1- to 2-week period. In this version of the ICSD-3, there are three persistent hypersomnolence disorders not associated with another illness or substance: narcolepsy type 1, narcolepsy type 2, and IH (Table 2).

The classic symptom tetrad for narcolepsy is EDS, cataplexy, sleep paralysis, and hallucinations at sleep onset or offset (ie, hypnagogic or hypnopompic hallucinations, respectively). Cataplexy is defined as the sudden loss of muscle tone in response to a strong emotion, most typically when hearing or telling a joke. However, < 10% of patients exhibit all symptoms initially and this may contribute to the average diagnostic delay of 10½ years.[11] Cataplexy is present in 65% to 75% of individuals with narcolepsy.[12-14] It is quite specific; only rarely will cataplexy or cataplexy-like episodes occur in other disorders, including Coffin-Lowry syndrome, Norrie disease, and Niemann-Pick disease type C.[15-19] The presence or absence of cataplexy is a key distinguishing feature between the two types of narcolepsy, which are now recognized to be quite different entities despite their similar nomenclature. Cataplexy is present in narcolepsy type 1 (formerly known as narcolepsy with cataplexy) and absent in narcolepsy type 2 (formerly narcolepsy without cataplexy) (Table 2). Many patients with narcolepsy type 1 have fragmented nocturnal sleep, underscoring the fact that this type of narcolepsy reflects difficulty with state control.[20] In essence, patients with narcolepsy type 1 have difficulty remaining awake when desired, but also, at times, with remaining asleep when it is alternately desired.

Cataplexy can also be conceptualized as a problem of state control, such that a feature of rapid eye movement (REM) sleep (ie, the paralysis, or atonia, that typically accompanies normal REM sleep) suddenly intrudes into wakefulness.[20] REM behavior disorder, in which patients are able to act out dreams because their motor control during REM more closely resembles that of wakefulness (ie, they have a lack of paralysis, or lack of atonia), is another disorder of sleep-wake state control that is common in narcolepsy type 1.[21] Sleep fragmentation may also be a common feature of narcolepsy type 2,[22] but is very atypical for IH.

The remaining features of the narcolepsy tetrad, sleep paralysis and hallucinations, are common in patients with either type of narcolepsy, but sleep paralysis also occurs in healthy subjects (5%-40%)[23] and these features do not reliably distinguish among the major hypersomnolence syndromes (Table 3).[24-38] Patients with IH have EDS but never cataplexy, and have a clinical presentation more similar to those patients with narcolepsy type 2 than type 1. Sleep paralysis and hallucinations are variably present in IH. One-third to two-thirds of patients with IH experience what Roth described as "sleep drunkenness": a prolonged state after awakening in which motor functions return before full awareness or there is partial return of both.[10,32,39] Patients report great difficulty

TABLE 1] Central Disorders of Hypersomnolence[10]

Disorders
Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnia
Kleine-Levin syndrome
Hypersomnia due to a medical disorder
Hypersomnia due to a medication or substance
Hypersomnia associated with a psychiatric disorder
Insufficient sleep syndrome

TABLE 2] *International Classification of Sleep Disorders, Third Edition*, Diagnostic Criteria[10]

Narcolepsy Type 1[a] Criteria A and B	Narcolepsy Type 2[b] All Criteria A-E	Idiopathic Hypersomnia[c] All Criteria A-F
A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 mo	A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 mo	A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 mo
B. Either 1 or 2 or both	B. Mean sleep latency ≤8 min and two or more SOREMPs on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs.	B. Fewer than two SOREMPs on MSLT (or fewer than one if nocturnal REM latency was ≤15 min)
1. Cataplexy and mean sleep latency ≤8 min and two or more SOREMPs on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs.	C. No cataplexy	C. No cataplexy
2. Low CSF hypocretin-1 concentration (<110 pg/mL or less than one-third of control values)	D. CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration is ≥110 pg/mL or greater than one-third of control values.	D. Either 1 or 2 or both
	E. The hypersomnolence and/or MSLT findings are not better explained by other causes.	1. Mean sleep latency ≤8 min on MSLT
		2. Total 24-h sleep time ≥660 min on 24-h polysomnographic monitoring or wrist actigraphy (averaged over ≥7 d)
		E. Insufficient sleep syndrome is ruled out.
		F. The hypersomnolence and/or MSLT findings are not better explained by other causes.

CSF = cerebral spinal fluid; MSLT = multiple sleep latency test; REM = rapid eye movement; SOREMP = sleep-onset rapid eye movement period.
[a]Formerly narcolepsy with cataplexy.
[b]Formerly narcolepsy without cataplexy.
[c]Formerly idiopathic hypersomnia with long sleep time and without long sleep time.

with awakening, requiring multiple alarms or specific procedures to awaken. Most patients with IH (75%) feel unrefreshed after naps, which are long.[32] In contrast to narcolepsy type 1, high sleep efficiency (≥90%) and occasional spontaneous remission are seen in IH.[26]

Given these overlapping clinical features, the diagnosis of hypersomnolence disorders requires attention to both clinical presentation and sleep testing, especially the multiple sleep latency test (MSLT). The MSLT consists of five 20-min nap opportunities at 2-h intervals.[40,41] The fifth nap opportunity is sometimes omitted in cases of narcolepsy where diagnostic criteria have been met after the first four naps.[41] A polysomnogram immediately precedes the MSLT to ensure a sufficient amount of sleep (≥6 h) and to rule out other sleep disorders, and sleep logs and/or actigraphy are recommended the week before to document habitual sleep times and rule out insufficient sleep. All stimulants and REM-suppressing medications should be discontinued 2 weeks before the test, although in practice, this may sometimes be difficult. The two parameters of most interest are the mean sleep latency (MSL) and the number of sleep-onset REM periods (SOREMPs). The sleep latency is the first epoch of sleep (any stage), and the MSL is the mean across all naps. A SOREMP is the presence of at least one epoch of REM during a nap opportunity. The MSLT is a major factor in current classification of patients with hypersomnolence disorders, such that the number of SOREMPs determines whether a patient with a clinical syndrome of hypersomnolence is classified as having narcolepsy (if they have two or more SOREMPs) or if

TABLE 3] Clinical Features of the Narcolepsies and Idiopathic Hypersomnia

Feature	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Excessive daytime sleepiness	Present	Present	Present
Cataplexy	Generally present (cataplexy plus characteristic MSLT features, or hypocretin deficiency, are necessary for diagnosis)	Absent (by definition)	Absent (by definition)
Sleep paralysis	Present in 69%[a]	Present in 35%[a]	Present in 20%[a]
Sleep hallucinations	Present in 77%[a]	Present in 42%[a]	Present in 25%[a]
Tetrad of all four of the above symptoms	Present in 42% (although not all present initially)[24]	Absent	Absent
Fragmented nocturnal sleep	Significantly lower sleep efficiency than narcolepsy without cataplexy[25] or idiopathic hypersomnia[26]	May be common[22]	Not typical
REM sleep behavior disorder	Present in 45%-61%[27]; significantly more PSG-measured REM sleep without atonia than in IH[28]	Significantly more PSG-measured REM sleep without atonia than in IH[28]	Rate of REM sleep behavior disorder not studied
Sleep drunkenness	Rare, but occasionally reported[26,29]	May be common[29]	Common
Long nocturnal sleep times	Present in 18% of patients with narcolepsy with or without cataplexy[30]	Present in 18% of patients with narcolepsy with or without cataplexy[30]	Common
Effect and duration of naps	Refreshing, short		Unrefreshing (compared with either patients with narcolepsy with cataplexy[31] or normal control subjects[32]), long

IH = idiopathic hypersomnia. See Table 2 legend for expansion of other abbreviations.
[a]Frequency estimates for sleep paralysis and hypnogogic hallucinations are compilations from case series reporting on at least two of the groups outlined in this table.[29,33-38]

they have IH (if they have fewer than two SOREMPs) (Table 2).

The MSLT has long been the gold standard for the diagnosis of narcolepsy, but like most diagnostic modalities, is not without flaws. First, neither short MSL nor SOREMPs are specific. Up to 30% of the normal population may have a MSL $\leq$ 8 min, the current cutoff for the hypersomnolence disorders.[42] Multiple SOREMPs can be seen in 3.9% to 9.5% of the general population,[43,44] although retest reliability of this (and other) MSLT parameter is poor on a population level.[45] Multiple SOREMPs are more common among shift workers and men.[44,45] Smaller studies have suggested that multiple SOREMPs may be observed in OSA,[46] Prader-Willi syndrome,[47] Parkinson disease,[48] and myotonic dystrophy.[49] Second, the MSLT may not be adequately sensitive, especially for IH. The 8-min cutoff was determined for patients with narcolepsy and extended to IH for "simplicity," without independent determination.[50] This arbitrary cutoff misses 22% to 39% of subjects who otherwise meet clinical criteria for hypersomnia, and up to 71% of those hypersomnolent patients with long sleep times (> 600 min).[51,52] Third, while MSLT test-retest reliability is high in patients with narcolepsy with cataplexy restudied within 3 weeks,[53] in clinical practice, test-retest reliability of the MSLT in narcolepsy without cataplexy and IH is poor. More than one-half of subjects with these disorders are given a changed diagnosis on repeat testing.[54]

There are several reasons why the MSLT may not accurately capture hypersomnolence. First, the subjective experience of sleepiness (on the Epworth Sleepiness Scale [ESS]) correlates only modestly with MSL.[55,56] Sleepiness is typically experienced as the inability to stay awake when desired, yet the MSLT measures "sleepability," or the ability to fall asleep on command. These two constructs, while related, are clearly not identical. Furthermore,

subjective sleepiness and MSL may not be equivalent because individuals can misperceive electrophysiologic sleep.[57] Second, the MSLT is affected by fluctuating physiologic levels of arousal that are distinct from sleepiness.[58] The MSLT is also affected by age: In patients with narcolepsy and cataplexy, older age correlates with higher MSL and fewer SOREMPs.[59] For all these reasons, it is imperative to interpret the MSLT in clinical context. The ICSD-3 retained diagnostic criteria using MSL, but specified that MSL is best considered as a continuum, with scores <5 min generally reflecting sleepiness and scores >10 min generally not.[10]

There are several important differences when compared with the second edition of the ICSD. The condition of hypersomnolence, or the state of excessive sleepiness, is clearly distinguished from the specific syndrome of hypersomnia. Narcolepsy is now subdivided into narcolepsy type 1 (characterized by either cataplexy and typical MSLT findings or low cerebrospinal fluid [CSF] hypocretin levels) and narcolepsy type 2 (lacking both cataplexy and low CSF hypocretin levels) (Table 3). This departure from prior nomenclature (narcolepsy with and without cataplexy) emphasizes the pathogenic role of hypocretin deficiency. While the diagnosis of narcolepsy still relies on the presence of REM sleep occurring shortly after sleep onset during MSLT (ie, SOREMPs), new criteria allow a nocturnal REM latency ≤ 15 min to count toward the two or more SOREMPs needed. A REM latency ≤ 15 min on a nocturnal polysomnogram is highly specific for narcolepsy with hypocretin deficiency or cataplexy (95%-99%) but not sensitive (36%-58%).[60]

Additionally, the ICSD-3 no longer distinguishes between IH with and without long sleep time. While the MSLT remains important in the diagnostic framework for IH, there is now a non-MSLT criterion based on measured sleep time of 660 min over 24 h, either through continuous polysomnography (PSG) or actigraphy. This might be expected to better capture the group of patients with a clinical picture of IH but an MSL >8 min. In patients with hypersomnia with a MSL <8 min or a documented 24-h sleep time ≥ 660 min, sleep time during 24-h PSG well differentiated patients from control subjects (525 min [SD, ± 87] in control subjects and 695 ± 99 in patients with IH).[51] However, in this study, 30 of 105 patients (29%) with suspected IH had both MSL >8 and sleep time <660. In a separate cohort of 98 subjects with hypersomnolence (excluding the two subjects with IH and habitual sleep time >10 h), patients who had a clinical phenotype of IH were indistinguishable on 24-h continuous PSG, regardless of whether they had an MSL <8 min or >8 min, and the sum of average night sleep plus average naps did not exceed 660 min in either group (493.9 min in those with MSL >8 min and 516.8 min in those with MSL <8 min).[61]

Optimal diagnostic methods for IH require further study. Given the limited face validity of the MSLT for capturing sleepiness, it has been suggested that the maintenance of wakefulness test (MWT), in which patients are asked to remain awake, may be useful. However, at present, this is not validated for IH or narcolepsy diagnosis. Within the MSLT itself, a longer sustained sleep latency, defined as the latency to either three stage-1 non-REM epochs or a single epoch of any other sleep stage, has been proposed as a possible marker to differentiate IH from the narcolepsies, but further validation is needed.[52] Other authors have found that transitions from N1 or wake directly into REM, without passing through N2, are very common in patients with narcolepsy type 1 (either during the MSLT or during the first REM period of the night), are completely absent in IH, and occur with an intermediate frequency in patients with narcolepsy type 2.[62,63]

The ICSD-3 contains diagnostic criteria for an additional five central hypersomnolence disorders (Table 1). The hypersomnolence syndromes that occur on a recurrent basis, rather than persistently, have now been consolidated into the single diagnosis of Kleine-Levin syndrome. This diagnosis requires at least two episodes of recurrent, time-limited hypersomnia (2 days to 5 weeks), associated with cognitive or perceptual dysfunction, disinhibition, or disordered eating, with return to normal baseline between events.

Epidemiology

The prevalence of narcolepsy with cataplexy is 0.025% to 0.05%.[12,64] Globally, the prevalence varies from highest in Japan (0.16%) to lowest in Israel (0.0002%).[65] The age of onset in clinical populations appears to be bimodal, with the first peak at 15 years and the second at 35 years,[66] although a population-based study demonstrated a single large peak between ages 10 and 19, with gradual tapering off with increasing age.[12] There are no population-based prevalence estimates for IH using the second edition of ICSD or ICSD-3 classifications,[1] so prevalence estimates are extrapolations from sleep disorders clinics. These estimates of the relative frequency of IH to narcolepsy with cataplexy vary substantially, from 1:10 to greater than 1:1.[25,26,29,34,52] This may reflect differing referral patterns, but makes it difficult to conclusively

estimate IH prevalence. The age of onset of IH symptoms ranges from the late teens to the mid 30s.[67] Unlike narcolepsy, spontaneous remission has been reported in 14% to 25% of patients with IH.[51]

Pathophysiology

The neuropeptide hypocretin (also called orexin) was first identified in 1998.[68,69] Hypocretin is produced in the lateral hypothalamus and is involved in the regulation of feeding, stress response, reward, and the autonomic nervous system.[70] Hypocretin is vital for the regulation of the sleep-wake cycle by its influence on the histaminergic, nonadrenergic, serotonergic, and cholinergic systems.[71] CSF hypocretin-1 levels are reduced in the majority (90%-95%) of subjects with narcolepsy and typical cataplexy.[72] While loss of hypocretin neurons is also seen in 10% to 30% of cases of narcolepsy without cataplexy, most patients with narcolepsy without cataplexy have normal hypocretin levels.[22]

The loss of hypocretin and development of narcolepsy type 1 involves both genetic and environmental factors, likely resulting from an autoimmune attack on hypocretin neurons in genetically susceptible individuals. The clear genetic predisposition is seen in the 10 to 40 times higher risk of narcolepsy in first-degree relatives of patients. Human leukocyte antigen (HLA) DQB1*06:02 is present in $>$ 85% to 95% of patients with typical cataplexy but is not specific, as it is also present in 40% of cases of narcolepsy without cataplexy and 24% of non-sleepy control subjects.[13] Genomewide association studies of narcolepsy have identified several risk alleles in additional genes involved with immune system functioning, including the T-cell receptor α locus (responsible for antigen recognition),[73] *P2RY11* (receptor expressed in $CD8^+$ cells),[74] cathepsin H (antigen processing and presentation on major histocompatibility complex molecules),[75] and *TNFSF4/OX40L* (costimulatory factor for T-cell activation).[75]

Despite this apparent genetic predisposition to narcolepsy, concordance rates in identical twins are only 25% to 31%,[76] implicating substantial environmental or stochastic factors. The occurrence of narcolepsy onset is seasonal (most frequent in April) in China, implicating a variable exposure, possibly infectious.[77] Narcolepsy incidence increased threefold to fourfold after the 2009-2010 H1N1 pandemic in China,[77] and particular versions of the adjuvanted H1N1 vaccine were associated with narcolepsy onset.[78] The increase in narcolepsy incidence after H1N1 vaccination in Europe ranged from a rate ratio of 1.9 (95% CI, 1.1-3.1) in Denmark to 7.5 (95% CI, 5.2-10.7) in Sweden, in the age group 5 to 19 years.[79] Other infections might trigger narcolepsy, as suggested by the presence of antistreptococcal antibodies in 65% of patients with narcolepsy within 1 year of disease onset (compared with 26% in age-matched control subjects),[80] and the observation that narcolepsy is 5.4 times more common in those individuals who are HLA DQB1*0602 positive with physician-diagnosed streptococcal infection than in individuals who are DQB1*0602 positive without childhood streptococcal infection.[81] The combination of HLA association, genetic polymorphisms in immune genes, and apparent triggering of disease by infection or vaccination all suggest an autoimmune basis for hypocretin-deficient narcolepsy, but this has yet to be conclusively demonstrated.[82]

The pathophysiologies of narcolepsy type 2 and IH are not yet known. A familial component has been proposed, as a family history of EDS is common in patients with IH, more so than in patients with narcolepsy with cataplexy.[5,25,83] The HLA DQB1*0602 allele implicated in narcolepsy has been shown to be increased in IH patients in some,[35] but not all,[34,51] investigations. Japanese subjects with "essential hypersomnia" (defined as the presence of excessive sleepiness in the absence of cataplexy or a condition such as sleep apnea that explains the sleepiness, which appears to be inclusive of the current ICSD-3 entities of narcolepsy type 2 and IH) also have increased positivity for the haplotype DRB1*1501-DQB1*0602.[84] An increased frequency of three HLA alleles in linkage disequilibrium—Cw2, DR5, and B27—and a decreased frequency of DRB1*11 have been reported in IH, but not across all studies.[51,85,86] A single genomewide association study of Japanese subjects with essential hypersomnia identified risk alleles in three genes: *NCKAP5*, *SPRED1*, and *CRAT*.[87] A single nucleotide polymorphism between *CPT1B* and *CHKB*, known to be overrepresented in patients with narcolepsy plus cataplexy,[88] is also more common in patients with essential hypersomnia than control subjects.[84] The role of these genes in predisposing or causing hypersomnolence remains to be determined.

Patients with IH may have low CSF histamine levels,[89] although this was not replicated.[36] Patients with IH may have higher total serum IgG levels than control subjects (in contrast to patients with narcolepsy with cataplexy who have lower total levels).[90] The authors speculated that this finding, as well as the distribution of IgG subclasses in patients with IH, might be related to sleep-associated cytokine production in patients with IH.[90]

Rye et al[9] studied CSF of 32 hypersomnolent patients and found a gain of function within the gamma-aminobutyric acid-A ($GABA_A$) system (ie, the presence of a positive allosteric modulator of $GABA_A$ receptors in patients more than control subjects). The effect on $GABA_A$ receptors could be reversed in vitro with flumazenil, a negative allosteric modulator of $GABA_A$ receptors, and IV flumazenil improved subjective sleepiness and measured vigilance in patients.[9] Case reports of two patients treated successfully with sublingual/transdermal[9] or subcutaneous[91] flumazenil over weeks to years further support the hypothesis that abnormal $GABA_A$ receptor activity may be contributing to sleepiness, but further work is needed to establish the possible role of the GABA system in hypersomnolence.

Treatment

In patients with hypersomnolence disorders, the goal of treatment is to curtail daytime sleepiness. In patients with narcolepsy type 1, treatment of cataplexy is also often desired. Nonpharmacologic measures may be helpful in reducing sleepiness in some patients. In particular, for patients with narcolepsy, the combination of scheduled naps and a regular bedtime may reduce daytime sleep time, especially in those patients who remain sleepy despite stimulant medication.[92] However, scheduled naps alone appear insufficient to control sleepiness as monotherapy (ie, without wake-promoting medication).[93] In patients with idiopathic hypersomnia, in whom naps tend to be long and unrefreshing, scheduling of naps as a treatment strategy tends to be less successful. Support for patient and family through organized patient advocacy and support groups is often reported by patients to be helpful in providing information and in combatting the sometimes negative public perception of people who are sleepy. Patients with narcolepsy, especially with cataplexy, are more likely than normal control subjects or patients with IH to be overweight or obese,[94-96] and so management of this comorbidity can be an important part of the treatment plan. OSA is also present in approximately 25% to 30% of patients with narcolepsy, although data are mixed regarding the potential benefit of CPAP on sleepiness in this group.[97-99] Patients with central disorders of hypersomnolence are at increased risk of motor vehicle accidents,[100,101] and counseling about this risk and the need to avoid driving while sleepy is very important. Regulations regarding driving with sleep disorders vary by state.

There are multiple US Food and Drug Administration (FDA) approved medications for narcolepsy and none for IH; medications for narcolepsy are frequently extended to off-label use in IH. Modafinil, a non-amphetamine, wakefulness-promoting agent, is considered standard therapy for EDS in narcolepsy by the American Academy of Sleep Medicine (AASM) (Table 4).[93] A meta-analysis of 1,054 patients with narcolepsy demonstrated that modafinil (200-600 mg/d) improved EDS relative to placebo, decreasing ESS by 2.73 points (95% CI, −3.39 to −2.08), increasing MSL on MSLT by 1.11 min (95% CI, 0.55-1.66), and increasing MSL on the MWT by 2.82 min (95% CI, 2.4-3.24).[102] Although both once-daily (morning) dosing and bid (morning and midday) dosing have been evaluated in randomized controlled trials (RCTs), split-dose regimens of modafinil taken bid appear more effective at controlling symptoms into the evening than single morning dosing.[103-105] Despite published use of dosages up to 600 mg/d,[102,106] the FDA-listed maximum dose in adults is 400 mg. Armodafinil, the longer half-life enantiomer of racemic modafinil, also significantly increases MSL on MWT compared with placebo in narcolepsy.[107] Armodafinil is typically dosed once daily (in the morning). Modafinil and armodafinil are also FDA-approved for the treatment of EDS in OSA syndrome and shift-work sleep disorder. Use of modafinil for IH has been based, until recently, on expert consensus,[93] but appears to have similar treatment benefit in IH and narcolepsy with cataplexy in clinical use (ESS change, -2.6 ± 5.1 in IH vs -3 ± 5.1 in narcolepsy).[108] In the first published RCT for EDS to include patients with IH, modafinil enhanced driving performance, increased sleep latency on MWT, and decreased subjective sleepiness compared with placebo.[109] Advantages of modafinil/armodafinil over traditional stimulants include low abuse potential and a generally better side effect profile. They are, however, associated with headache, nausea, and anxiety, which sometimes abate over time. Postmarketing data revealed rare cases of serious or life-threatening rash (Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms).[110] Although these medications are not FDA approved for pediatric use, they are used off-label in this population.[106] Their interaction with oral contraception (decreasing contraception efficacy) is important to consider in women of childbearing potential.

Sympathomimetic stimulants such as methylphenidate and dextroamphetamine are also effective for daytime sleepiness, but do have possible adverse psychiatric and cardiovascular effects.[111] Amphetamines have been used for narcolepsy since 1935,[112] and do increase MSL (from 4.3 to 9.3 min) and decrease errors on driving simulations (from 2.53% to 0.33%).[113] Methylphenidate relieves subjective

TABLE 4] Current and Future Treatment Options for Narcolepsy and Idiopathic Hypersomnia

Medication	Disorder	AASM Recommendation[a] or Level of Evidence if No Recommendation
For treatment of daytime sleepiness		
Modafinil	Narcolepsy	Narcolepsy: standard
	IH	IH: option, but RCT published subsequent to recommendation
Armodafinil	Narcolepsy	See recommendation for modafinil
	IH	...
Sodium oxybate	Narcolepsy	Standard (for both sleepiness and cataplexy)
Amphetamine, methamphetamine, dextroamphetamine, methylphenidate	Narcolepsy	Narcolepsy: guideline
	IH	IH: option
Ritanserin (not available in United States)	Narcolepsy	Option
Selegiline	Narcolepsy	Option (for both sleepiness and cataplexy)
Pitolisant (not available in the United States)	Narcolepsy	Narcolepsy: RCT published subsequent to recommendation (RCT to evaluate effect on cataplexy is ongoing)
	IH	IH: clinical case series
Clarithromycin	Narcolepsy type 2	Clinical case series (RCT results pending)
	IH	Clinical case series (RCT results pending)
Levothyroxine	IH (with long sleep time)	Clinical case series
For treatment of cataplexy		
Sodium oxybate	Narcolepsy	Standard (for both sleepiness and cataplexy)
Venlafaxine, SSRIs, tricyclic antidepressants, reboxetine (not available in the United States)	Narcolepsy	Guideline
Selegiline	Narcolepsy	Option (for both sleepiness and cataplexy)

AASM = American Academy of Sleep Medicine; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor. See Table 2 legend for expansion of other abbreviation.

[a] AASM recommendations follow these criteria: "Standard" refers to an accepted treatment reflecting high-quality evidence (highest recommendation); "guideline" refers a treatment supported by level 2 or substantial level 3 evidence (middle level of recommendation); "option" refers to a treatment with conflicting (or inconclusive) evidence or expert opinion (lowest level of recommendation).[93]

sleepiness and improves the ability to stay awake on the MWT.[114] These agents have been given a guideline recommendation for the treatment of EDS by the AASM.[93] Clinical series suggest that wake-promoting medications are successful in 62% to 83% of subjects with IH,[26,67,85] with a clinically challenging subgroup remaining refractory to these standard treatments.

Sodium oxybate, the sodium salt of γ-hydroxybutryrate, is considered a standard therapy for EDS, cataplexy, and disrupted sleep in narcolepsy by the AASM.[93] In meta-analysis, it was superior to placebo in reducing mean weekly cataplexy attacks by 8.5 (95% CI, −15.3 to −1.6), increasing MWT latency by 5.18 min (95% CI, 2.59-7.78), and reducing sleep attacks by 9.65 (95% CI, −17.72 to −1.59).[115] Modafinil and sodium oxybate may have additive effects on EDS.[116] The nightly divided dose of sodium oxybate can be burdensome for patients. Because of abuse potential and possible adverse effects (ie, deep sedation, respiratory depression), sodium oxybate is dispensed through a central pharmacy after thorough patient education.

Cataplexy can also be treated with REM-suppressing antidepressants, which are often used as first-line agents, although evidence is limited.[117] Tricyclic antidepressants have been used for several decades,[118] but may have adverse anticholinergic effects. Serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs) may also control cataplexy. Venlafaxine is a preferred cataplexy treatment, considering its benefit to risk ratio.[119,120] Tricyclics, SSRIs, and venlafaxine may also treat sleep paralysis and hypnagogic hallucinations.[93]

The treatment of the central disorders of hypersomnolence during pregnancy is complicated by a lack of available evidence regarding medication safety. The majority of agents are in FDA pregnancy category C, meaning either an absence of both human and animal safety data or evidence for harm in animal studies but absent human studies. Although no published guidelines exist for the treatment of narcolepsy during pregnancy, Thorpy et al[121] summarized the animal and human data on these medications, which may be helpful to clinicians in guiding therapy decisions. Pregnancy registries, which compile data from women exposed to specific medications during pregnancy, are currently available for modafinil and armodafinil, and the FDA maintains an updated list of all medications for which such registries exist.[122]

Novel therapies are under development for narcolepsy and IH. Hypocretin agonists administered via the intranasal route had have some limited success to date.[123] Pitolisant, a histamine-3 receptor inverse agonist, stimulates histamine release and promotes wakefulness. In a randomized trial of 95 patients with narcolepsy, it was superior to placebo in reducing ESS and increasing MWT latencies, although noninferiority to modafinil could not be demonstrated.[124] Pitolisant has been used with some success in patients with treatment-refractory IH,[125] but is not currently available in the United States. Based on the suspected autoimmune pathophysiology of type 1 narcolepsy, individual patients have been given IV immunoglobulin. Pooling data from these published cases, Knudsen et al[126] proposed that IV immunoglobulin may be useful for cataplexy and sleepiness in patients whose disease duration at the time of treatment is $\leq$ 9 months, although they tempered their conclusion, due to lack of a placebo-controlled trial.

Based on the findings that hypersomnolent patients demonstrate a positive allosteric modulator of $GABA_A$ receptors in their CSF,[9] and that clarithromycin is a negative allosteric modulator of $GABA_A$ receptors,[127] Trotti et al[128] reported the clinical use of clarithromycin in 53 subjects with central hypersomnolence disorders (without cataplexy). Sixty-four percent of these subjects, who had failed an average of 2.6 prior wake-promoting medications, reported improved EDS. Full results from a randomized, placebo-controlled trial of clarithromycin for hypersomnolence are pending publication, but data from the study, published in abstract form, confirmed a significant benefit on subjective sleepiness (a four-point greater reduction in the ESS with clarithromycin than with placebo).[129] Low-dose levothyroxine was beneficial in a small series of patients with IH with normal thyroid function.[130] Bupropion decreases sleepiness associated with depression[131] and, in our experience, may be helpful adjunct therapy in hypersomnolent patients even in the absence of depression.

Conclusions

Over the last 2 decades, there have been major advances in understanding the neurobiology of hypersomnolence. This is especially true for narcolepsy type 1, which now appears to result from a genetic predisposition interacting with environmental factors to trigger loss of hypocretin-containing neurons. Several genetic, immunologic, and biochemical abnormalities have been identified in subjects with narcolepsy type 2 and/or IH, although the full pathophysiology remains to be elucidated. Of the abnormalities documented to date, the CSF constituent that leads to excess $GABA_A$ receptor potentiation might have the most immediate treatment implications, but additional work is needed before GABA receptor modulators are considered for routine hypersomnolence treatment. Current diagnostic criteria are helpful but imperfect, and more sensitive and specific tests are needed. Effective treatments are available for many patients, but a treatment-refractory subgroup remains. Further research is essential to understand the biology and optimal management of these disorders.

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