Narcolepsy and Idiopathic Hypersomnia

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KEYWORDS

• Pediatric • Narcolepsy • Hypersomnia • MSLT

KEY POINTS

- Central disorders of hypersomnolence, including narcolepsy type1 and 2 and idiopathic hypersomnia, often have onset in childhood or adolescence but diagnosis is commonly delayed. Recognition of symptoms of these disorders will improve timeliness and accuracy of diagnoses.
- A clinical history including sleep timing, sleep duration, naps, and associated sleep symptoms may help differentiate sleep disorders.
- An overnight polysomnogram (PSG) and daytime multiple sleep latency testing (MSLT) or cerebrospinal fluid orexin testing is the gold standard for narcolepsy type 1; however, this PSG/MSLT sleep study testing has poor reliability in adults with narcolepsy type 2 and idiopathic hypersomnia.
- Insufficient sleep, circadian rhythm disorders, and certain medications may contribute to false-positive results on the multiple sleep latency test.
- There is no cure for narcolepsy or idiopathic hypersomnia; behavioral and pharmacologic treatments aim to reduce sleepiness and cataplexy and improve function.

INTRODUCTION

Narcolepsy types 1 and 2 and idiopathic hypersomnia are debilitating primary central nervous system disorders of hypersomnolence characterized by daytime sleepiness and/or excessive sleep need. Although the pathophysiology of narcolepsy type 2 and idiopathic hypersomnia has not been elucidated, narcolepsy type 1 develops due to a presumed autoimmune-mediated loss of orexin neurons in the lateral hypothalamus. These disorders often have onset in childhood or adolescence, and the presentation of sleepiness and cataplexy (a symptom of narcolepsy type 1) in children can manifest differently than in adults. The goal of this review is to describe a clinical approach, diagnostic evaluation, and management of children and adolescents with excessive daytime sleepiness due narcolepsy types 1 and 2, and idiopathic hypersomnia.

Initial Approach to the Sleepy Child/Adolescent

The International Classification of Sleep Disorders, version 3 (ICSD3) defines hypersomnolence as the irrepressible need to sleep or episodes of daytime sleepiness.[1] The first challenge of identifying central disorders of hypersomnolence in children and adolescents is evaluating the degree and pattern of excessive daytime sleepiness. The experience and description of sleepiness are subjective but most report falling asleep or feeling drowsy in passive situations (ie, reading, in classroom lecture, being driven, waiting patiently) and more rarely sudden sleep attacks. Sleepiness in children may manifest differently than in adults. Sleepy children may have hyperactivity, irritability, inattention, or emotional lability.[2,3] The Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD)[4] or the Pediatric Daytime Sleepiness Scale

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(PDSS)[5] can be quickly administered and are commonly used in the Sleep Clinic to evaluate propensity of dozing off in certain situations to both help differentiate "sleepiness" from "fatigue" and assess severity of daytime sleepiness. The Pediatric Hypersomnolence Survey (PHS) is a newly published pediatric hypersomnolence screening survey for ages 8 to 18 years freely available with 81% sensitivity and 81% specificity for narcolepsy or idiopathic hypersomnia[6] (**Fig. 1**, Supplementary Materials 1). This survey can help health-care practitioners direct referrals to sleep clinic and/or order appropriate diagnostic testing for more timely diagnoses.

Excessive daytime sleepiness is a common complaint among adolescents in particular making it difficult to tease out those with more chronic and severe complaints. In a survey of 6483 teens (13–18 years) in the United States, a staggering 41.5% reported excessive daytime sleepiness.[7] The American Academy of Sleep Medicine published sleep duration by ages: children aged 6 to

You are being asked questions about symptoms of a possible sleep problem. Think about your last week while you were in school when choosing your answers.

Check "Often" if the symptom happens 3 times or more per week. Check "Sometimes" if the symptoms happens 1–3 times per week Check "Never" if you do not have the symptom.

Check "DNK" for do not know if you are not sure if you have the symptom.

	Often (3) (> 3/week)	Sometimes (2) (1–3/week)	Never (1) (Never noted)	DNK (0) (Do not know)
1. I fall asleep in class	☐	☐	☐	☐
2. I miss things in class because I am sleepy	☐	☐	☐	☐
3. My friends tell me I fall asleep easily	☐	☐	☐	☐
4. I fall asleep in the bus/car after school	☐	☐	☐	☐
5. I ask to go to the nurse's office or somewhere quiet to sleep during the school day	☐	☐	☐	☐
6. I feel weak in the knees when I laugh with my friends	☐	☐	☐	☐
7. My voice slurs when I laugh hard	☐	☐	☐	☐
8. My body feels weak briefly when I get excited or laugh	☐	☐	☐	☐
9. I dream when I sleep at night	☐	☐	☐	☐
10. My dreams seem very real	☐	☐	☐	☐
11. When I wake up, I can't move for a few minutes	☐	☐	☐	☐
12. I write silly things when taking notes in class because I am sleepy	☐	☐	☐	☐
13. It takes me a long time to do my homework because I am so tired	☐	☐	☐	☐
14. Doing homework makes me tired	☐	☐	☐	☐

Fig. 1. PHS. The full PHS and instructions can be found in Supplemental Material. Score "Often" = 3 points, "Sometime" = 2 points, "Never" = 1 point. "Do not know" responses may require further clarification/explanation about symptoms queried by the provider. A Total Score greater than 24 suggests high risk for narcolepsy or idiopathic hypersomnia. The Sleepiness Subscore (Questions 1–5 and 12) greater than 8 suggests severe daytime sleepiness and is more sensitive for idiopathic hypersomnia diagnosis than the total score. (Maski K, Worhach J, Steinhart E, et al. Development and Validation of the Pediatric Hypersomnolence Survey. Neurology. 2022;98(19):e1964-e1975.)

12 years should sleep 9 to 12 hours and teens should sleep 8 to 10 hours per 24 hours on a regular basis to promote optimal health.[8] Obtaining a clear record of habitual sleep patterns from children and caregivers, including bedtime, wake time, nap times, and sleep duration over a 2-week period (including weekdays and weekends) is necessary to distinguish disorders of hypersomnolence from more common causes of sleepiness such as insufficient sleep or circadian rhythm disorders in children and adolescents. Sleep diaries or sleep logs[9] are required for this purpose but more ideally actigraphy testing (a wristwatch device that objectively identifies sleep and wake based on motion) would also be used to ensure adequate sleep is objectively present before further diagnostic testing.[1] It is important to correct insufficient sleep or circadian rhythms disorders before sleep study testing to avoid false positives for narcolepsy or idiopathic hypersomnia. For instance, Carskadan and colleagues[10] found 2 or more sleep onset rapid eye movement (REM) periods on the multiple sleep latency testing (MSLT), a criterion for narcolepsy diagnoses, in 16% of tenth grade participants with delayed circadian rhythm. Similarly, obtaining detailed descriptions of the timing, frequency, and features of naps can be helpful to differentiate between narcolepsy and idiopathic hypersomnia. For instance, a teen who sleeps 6 hours at night and takes a 2-hour nap on returning home from school is more likely to have insufficient nocturnal sleep than a teen who habitually sleeps 8 hours at night and still requires a daytime nap(s).

Narcolepsy

Clinical features

Narcolepsy type 1 and 2 are chronic neurologic disorders characterized by symptoms of excessive daytime sleepiness, sleep-related hallucinations, sleep paralysis, disrupted nocturnal sleep, and cataplexy (in narcolepsy type 1 only; **Table 1**). Children and adolescents with narcolepsy also have abnormal physiology during sleep including findings of early entry into REM sleep after sleep onset,[11–13] a lack of the typical paralysis of REM sleep (REM sleep without atonia),[14–16] and REM sleep behavior disorder.[14] Investigators report that nearly one-third of children and adolescents with narcolepsy type 1 had REM behavior disorder with complex behavior or "pantomime-like behavior" reflecting true dream enactment. Thus, atypical parasomnia behavior presenting with stereotypical gestures, dream enactment, laughing, and/or talking that occurs throughout the night may be presenting REM behavior disorder in narcolepsy type 1 in contrast to non-rapid eye movement NREM disorders of arousals, which typically present with confused, nonpurposeful behavior in the first third of the night.

Narcolepsy type 1 can be differentiated clinically from narcolepsy type 2 by the presence of cataplexy. Cataplexy is generalized or partial loss of muscle tone, typically triggered by strong positive emotion, including laughter, surprise, or anticipation. The weakness of cataplexy may represent intrusion of REM muscle atonia into wake.[17] Generalized cataplexy, involving most of the body, seems as slumping, melting, or slouching to the floor. More commonly, cataplexy is partial, with face, neck, or limb involvement, appearing as droopy eyelids, slurred speech, or head drop.[18] Typical cataplexy features are (1) bilateral, symmetric lasting less than 2 minutes, (2) provoked by strong emotion particularly of positive nature (ie, laughter), (3) abrupt return of muscle activity after the episode, and (4) retained consciousness.[19] Children may also have "cataplexy facies," spontaneous and prolonged hypotonic attacks of the face, jaw, and eyelids associated with tongue protrusion.[20,21] Even more rarely, pediatric cataplexy can present with positive motor activity, such as phasic muscle twitches or dyskinesias; such behavior may resemble complex motor tics with repetitive mouth opening or tongue thrusting.[21–23] Additional atypical presentations of cataplexy include static tongue protrusion, ptosis, or gait instability.[21] "Status cataplecticus" is rare state of prolonged cataplexy, lasting hours, that typically occurs following abrupt withdrawal of cataplexy-suppressing medications or in the setting of insufficient sleep and has been reported in pediatric narcolepsy type 1.[14] Symptoms of daytime sleepiness typically precede or co-occur with the first episode of cataplexy. Cataplexy can occur years and even decades after onset of daytime sleepiness and notably delayed cataplexy is reportedly more common among African-American patients.[24,25] Thus, a patient could be initially diagnosed with narcolepsy type 2 and later convert to the diagnosis of narcolepsy type 1 emphasizing the importance of continually asking about the development of cataplexy in the type 2 cohort. A clinical description consistent with cataplexy should immediately raise concern for this diagnosis (**Box 1**).

Children and adolescents with both narcolepsy type 1 and type 2 describe episodic sleep paralysis, sleep-related hallucinations, and vivid dreams or dream-reality confusion. Sleep paralysis is the inability to move arms or legs for a few minutes, typically on waking from sleep, and can be present in up to 60% of people with narcolepsy.[26] People

Table 1
Clinical characteristics and diagnostic evaluation of central disorders of hypersomnolence

	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Clinical features			
Symptom pattern	Chronic	Chronic	Chronic
Excessive daytime sleepiness	Always	Always	Always
Cataplexy	Often	Never	Never
Sleep-related hallucinations	Often	Less common	Occasional
Sleep paralysis	Often	Less common	Occasional
Disrupted nighttime sleep	Often	Less common	Rare
Prolonged sleep duration	Rare	Occasional	Often
Sleep inertia	Rare	Occasional	Often
Daytime naps	Often: brief, refreshing	Variable	Often: long, unrefreshing
Diagnostic testing			
PSG/MSLT	Sleep latency ≤8 min 2 or more SOREMPs	Sleep latency ≤8 min 2 or more SOREMPs	Sleep latency ≤ 8 min 1–1 SOREMPs Alternative: ≥11 h in 24-h PSG, or average ≥ 11 h over 1-wk actigraphy
CSF Orexin (hypocretin)	Low (<110 pg/mL)	Normal, sometimes intermediate	Normal (usually >200 pg/mL)

Abbreviations: CSF, cerebrospinal fluid; MSLT, multiple sleep latency test; PSG, polysomnography; SOREMP, sleep-onset REM period.

retain full recall of the event and are completely aware during sleep paralysis and some people may describe a sensation of someone sitting on them or preventing them from moving. As sleep paralysis can occur with sleep-related hallucinations, it can be distressing. Sleep paralysis is more common in narcolepsy type 1 than in narcolepsy type 2, and is rarer, although can be seen, in idiopathic hypersomnia.[27,28] Sleep-related hallucinations while falling asleep (hypnogogic) or waking up (hypnopompic) are similarly described in both narcolepsy types 1 and 2 and less commonly with idiopathic hypersomnia.[27,28] Hallucinations are typically visual but auditory and somatic hallucinations have also been reported by people with narcolepsy. Children and adolescents may report shadowy figures in the room, animals, or formed shapes at the time of falling asleep or waking up.[29] Sleep paralysis and sleep-related hallucinations can be described in otherwise healthy sleepers experiencing sleep deprivation and/or severe sleep disruption.[30,31] The narcolepsy "tetrad" of sleepiness, cataplexy, sleep paralysis, and sleep-related hallucinations is present in only about 45% of people with narcolepsy type 1, and all 4 features are rarely present at the same time at the initial clinical evaluation.[28] Dream–reality confusion and vivid or lucid dreams (dreams during which a person is consciously aware of dreaming) are also reported by people with narcolepsy.[32] Occasionally, these dreams in people with narcolepsy are so realistic that they produce false memories of the dreamt events.[33] At time of symptom onset, children and adolescents with narcolepsy can have prolonged sleep duration but this normalizes with time to age-appropriate amounts of sleep.[34] Typically, children and adolescents with narcolepsy report daytime naps feel refreshing especially when naps are brief (<20 minutes).

Disrupted nocturnal sleep is a central feature of narcolepsy[35] and is enabled by intrinsic sleep instability associated with orexin (hypocretin) insufficiency.[36,37] The true prevalence of disrupted nighttime sleep in narcolepsy depends on how it is defined. Based on self-report, nearly 50% of children with narcolepsy type 1 report disrupted nighttime sleep.[38] People with narcolepsy have increased arousal index, sleep stage transitions, NREM stage 1 sleep (N1, light sleep), and wake after sleep onset time relative to healthy sleepers, subjectively sleepy controls, and people with

Box 1
Clinical features and causes of cataplexy in children and adolescents

Presentation of cataplexy:
- Bilateral, usually symmetric weakness of face, neck, limbs
  - Partial: eyelids drooping, slurred speech, head drop
  - General: slouching or slumping to the floor/seated position
- Atypical or positive movements:
  - Dyskinetic movements or phasic muscle twitching
  - Cataplexy facies
  - Status cataplecticus
- Decreased/absent reflexes in affected areas
- Lasts seconds to minutes
- Fully conscious, full event recall
- Triggered by strong emotion (usually positive: laughter, anticipation)

Causes:
- Strongly associated with narcolepsy type 1
- Also seen in:
  - Niemann-Pick type C Disease
  - Angelman syndrome
  - Norrie disease
  - Prader-Willi syndrome
  - Myotonic dystrophy
  - Hypothalamic lesions: stroke, trauma, malignancy, infectious, inflammatory

idiopathic hypersomnia.[39–42] There is lower overall sleep efficiency in narcolepsy type 1 than either narcolepsy type 2 or idiopathic hypersomnia.[43] In particular, REM and NREM stage 2 (N2) sleep are particularly unstable in pediatric narcolepsy type 1, whereas children and adolescents with narcolepsy type 2 have more stable N1 sleep compared with subjectively sleepy controls.[41] Overall, people with narcolepsy type 2 can have clinically intermediate symptoms, with lower rates of sleep paralysis, sleep-related hallucinations, and disrupted nocturnal sleep when compared with narcolepsy type 1 (although elevated rates of these symptoms relative to healthy sleepers).[27]

Epidemiology

The prevalence of narcolepsy type 1 is estimated to be about 1:2000, or 0.05%[44] and affects men and women equally. Age of onset is bimodal with peaks at about 15 and 35 years of age[45]; however, there is often considerable delay between symptom onset and diagnosis with median time to diagnosis as high as 10 years.[46,47] Although historically the incidence of narcolepsy type 1 was greater than narcolepsy type 2,[48,49] a recent review of the United States population showed that narcolepsy type 2 is 4.7 time more diagnosed than narcolepsy type 1 with higher reporting of women having narcolepsy type 2.[50]

Pathophysiology

Narcolepsy type 1 is caused by immune-mediated selective loss of orexin (hypocretin)-producing neurons in the hypothalamus.[51] Orexin (hypocretin) is a peptide that promotes wake and coordinates sleep-stage transition stability. In narcolepsy type 1, neuronal loss is specific to the orexin (hypocretin) neurons within the hypothalamus and even intermingling melanin-concentrating hormone neurons remain preserved.[51] Evidence supporting immune-mediated loss of these neurons includes association with specific HLA alleles (the strongest association with DQB1*0602)[52] and identification of activated T cells in people with narcolepsy type 1.[53] Additionally, there are associations of narcolepsy type 1 with T cell function identified on genome-wide association study, including components of T-cell antigen presentation and recognition.[54] Increase in narcolepsy type 1 incidence in spring (after winter virus season),[55] associations with H1N1 infection and a specific version of the H1N1 vaccine used in Europe,[56] and associations with other infectious titers further support immune-mediated cause.[52]

Narcolepsy type 2 is a clinically heterogenous disorder, and the physiology is unclear. A subset of people (about 20%) initially diagnosed with narcolepsy type 2 eventually develop orexin (hypocretin) deficiency,[57] suggesting this is an intermediate diagnosis for some. For most people with narcolepsy type 2, orexin (hypocretin) levels are normal, although there may be partial loss of orexin (hypocretin) neurons as reflected by mildly lower cerebrospinal fluid (CSF) orexin (hypocretin) levels than normal.[58]

Common comorbidities

Children and adolescents with narcolepsy often have increased risk of medical, sleep, and psychiatric comorbidities complicating disease course and treatment. Obesity is markedly high among children and adolescents with narcolepsy with prevalence of up to 74%.[59,60] In another study, additional metabolic derangements have been reported among people with narcolepsy including

increased findings of diabetes mellitus, hypertension, and dyslipidemia[61] that may increase later cardiovascular risks. Independent of obesity, investigators report precocious puberty in 17% of children and adolescents with narcolepsy.[60] Other comorbidities reported in adults with narcolepsy include thyroid dyscrasias, nonmigranous headaches, peripheral neuropathy, and chronic low back pain.[62] Sleep disorders, including obstructive sleep apnea, periodic limb movement disorder, and REM behavior disorder also have increased incidence in people with narcolepsy.[63] Psychiatric and behavioral comorbidities associated with narcolepsy include depression, anxiety, attention deficit hyperactivity disorder (ADHD), or obsessive-compulsive disorder; these conditions often persist despite treatment of daytime sleepiness.[64,65] In one study, rates of clinically significant ADHD were 15% in children and adolescents with narcolepsy type 1 and 30% in children and adolescents with narcolepsy type 2, compared with 5% to 6% of controls.[64] Given narcolepsy medication treatments can have psychiatric adverse effects, clinicians must closely monitor children and adolescents with narcolepsy for worsening or new onset mood disorders and suicidality.

Secondary narcolepsy

Cases of secondary narcolepsy or genetic conditions causing cataplexy should also be considered in the correct clinical context. Damage of the orexin (hypocretin) neurons or their projections by trauma, malignancy, inflammation, or infection can cause secondary narcolepsy with or without cataplexy in both adults and children.[66–70] Children and adolescents with cataplexy who have focal neurologic deficits or encephalopathy merit further evaluation, minimally, with brain MRI to evaluate for secondary narcolepsy. Cataplexy can be seen in neurogenetic syndromes: Niemann-Pick type C, Angelman syndrome, Norrie disease, Prader-Willi syndrome, myotonic dystrophy, and DNA methyltransferase-1 (DNMT1)-complex disorder.[71–74]

Idiopathic Hypersomnia

Clinical features

Idiopathic hypersomnia is clinically characterized by excessive daytime sleepiness, severe difficulty waking from sleep (sleep inertia), and daytime "brain fog" or cognitive cloudiness. Descriptions of the daytime sleepiness in idiopathic hypersomnia range from mild to severe and additionally, people frequently report fatigue or low energy. People with idiopathic hypersomnia can have prolonged sleep duration with more than 10 to 11 hours of habitual nocturnal sleep plus long daytime naps, yet they still report unrefreshing sleep and not feeling rested after naps[75,76] in contrast to people with narcolepsy.

Sleep inertia, or difficulty rising from sleep in the morning, is a common complaint in idiopathic hypersomnia.[77] Sleep inertia is brief in healthy sleepers[78] but in people with idiopathic hypersomnia, this period is both prolonged and pronounced. People with idiopathic hypersomnia may require multiple alarms and intervention of a family member to get them out of bed in the morning.[79] Sleep inertia in idiopathic hypersomnia is also referred to as sleep drunkenness,[80] due to cognitive dysfunction and sometimes clumsiness of movements.

Epidemiology

Idiopathic hypersomnia is thought to be a rare disease, although estimated prevalence is limited by heterogeneous symptoms; it is estimated to be about one-tenth to one-half as common as narcolepsy with 20 to 50 cases per million.[75,81–83] Symptoms often begin in the second decade, with mean onset of symptoms 19.1 years (SD 11.3 years) reported in an idiopathic hypersomnia patient registry.[84] A subset of people with idiopathic hypersomnia report symptom onset after a preceding illness or minor head trauma.[75,81] Based on a disease registry study, people with idiopathic hypersomnia tend to be female and Caucasian but demographics may be misrepresented based on survey respondents.[84]

Pathophysiology

The pathophysiology of idiopathic hypersomnia is unknown as its name implies. There are several hypotheses regarding possible mechanisms that may underlie symptoms of idiopathic hypersomnia, including enhanced gamma-aminobutyric acid (GABA) responsiveness, autonomic dysfunction, or circadian disruption. People with idiopathic hypersomnia (as well as other hypersomnia conditions) have shown increased GABA-A receptor potentiation relative to controls[85] although findings are not consistent in the literature.[86] In clinical trials, medications that modulate GABA-A receptor activity decrease sleepiness in some people with idiopathic hypersomnia.[87,88] Dysautonomia may underlie idiopathic hypersomnia physiology: people with idiopathic hypersomnia have increased autonomic symptoms relative to controls.[79,89] There is also evidence of increase in the ratio of parasympathetic to sympathetic activity in idiopathic hypersomnia in a study of heart rate variability.[90] Another hypothesis is that idiopathic hypersomnia represents a circadian rhythm disorder, with data supporting a "long biologic night."

Skin fibroblasts from people with idiopathic hypersomnia have prolonged circadian period length relative to controls[91] and decreased amplitude of circadian gene expression.[92] A challenge in identifying the cause of idiopathic hypersomnia may be the heterogeneity in the patient population but possibly there are diverse pathophysiology and mechanisms resulting in a common phenotype.

There is ongoing discussion regarding the relationship between narcolepsy type 2 and idiopathic hypersomnia, and a subset of these people (especially those with normal sleep duration) may share common physiology.[93] Currently diagnostic differentiation between these conditions is reliant on the presence of 2 or more sleep onset REM periods (SOREMPs) on the polysomnogram (PSG) and MSLT (detailed further below) for narcolepsy. However, the MSLT test-retest reliability can be poor in adults with idiopathic hypersomnia and narcolepsy type 2[94–96] and therefore difficulties differentiating these conditions may be due to testing limitations. It is unknown if similar MSLT reliability issues are present in pediatric patient populations.

DIAGNOSTIC TOOLS AND EVALUATION FOR NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA

In addition to the sleep history, disorders of hypersomnolence are most commonly diagnosed by overnight PSG followed by the MSLT. The overnight PSG helps to exclude factors that contribute to daytime sleepiness, such as sleep apnea or sleep deprivation (a minimum of 6 hours of sleep is required on overnight PSG to proceed with the MSLT), and to record REM sleep latency because this may be used toward the diagnosis of narcolepsy. The MSLT consists of five 20-minute nap opportunities every 2 hours throughout the day (**Fig. 2**) and measures sleep latency and SOREMPs. A mean sleep onset latency consistent with hypersomnolence is defined as less than or equal to 8 minutes in both narcolepsy and idiopathic hypersomnia. A sleep onset REM period is defined as the onset of REM sleep occurring within 15 minutes of falling asleep (SOREMP). Narcolepsy is distinguished from idiopathic hypersomnia by the presence of 2 or more SOREMPs in either the nap opportunities of the MSLT or the beginning of the overnight PSG (nocturnal SOREMP). In a study of children and adolescents undergoing evaluation for suspected narcolepsy, at least 2 SOREMPs *or* a mean sleep latency less than or equal to 8.2 minutes on the MSLT were reliable markers for pediatric narcolepsy type 1.[97] The nocturnal SOREMP is an important biomarker for adults and children with narcolepsy with cataplexy with high specificity (97%) but relatively poor sensitivity less than 60%.[11,13] The high specificity of this nocturnal SOREMP biomarker permits diagnosis of narcolepsy with only PSG alone in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[98]

Several scenarios can result in a false-positive PSG-MSLT testing. In particular, habitual sleep timings (weekdays and weekends) and duration can influence results as noted in the "Initial Approach to the Sleepy Child/Adolescent" section. Actigraphy or sleep logs should be obtained for the 2 weeks leading up to the sleep study.[99] Further, medications impact sleep architecture and can influence the MSLT. Medications that are sedating or alerting can impact sleep onset latency. SOREMPs can also be influenced by medications, most commonly selective serotonin reuptake inhibitors (SSRI) antidepressants, which suppress REM sleep.[100,101] In a pediatric study of MSLT outcomes, patients on REM-suppressing antidepressants had fewer SOREMPs than those not taking these medications.[102] Of note, withdrawal effects of REM-suppressing antidepressants with an advanced taper can influence the MSLT by increasing the numbers of MSLT SOREMPs and reducing mean sleep latency.[102] Tapering REM-suppressing medications are less important for the evaluation of idiopathic hypersomnia because REM abnormalities are not part of the diagnostic criteria. Optimally, any medications that impact sleep propensity and sleep architecture should be tapered before testing; whereas 2-weeks is recommended for most antidepressants,[103] and this may not be sufficient for medications with longer half-lives such as fluoxetine. Illicit drug use and withdrawal as well as caffeine use can also influence sleep latency and REM sleep,[104,105] so urine toxicology screening is routinely obtained on the morning of the MSLT.

To address these many contextual influencers, the American Academy of Sleep Medicine developed updated 2021 practice parameters to guide testing.[99] These include guidelines for the study night, as well as preparation. Specifically, the guidelines recommend a 2-week activity/sleep log (and actigraphy when able) and 2-week tapering off of REM suppressing/sleep altering medications. These guidelines also recommend the MSLT report author detail medication used or recently discontinued on the MSLT report to improve transparency of potentially confounding factors for clinical interpretation.[99] Overall, the MSLT has high diagnostic validity and reliability for people with narcolepsy type 1[95]; however, there is more variability for diagnosis of narcolepsy

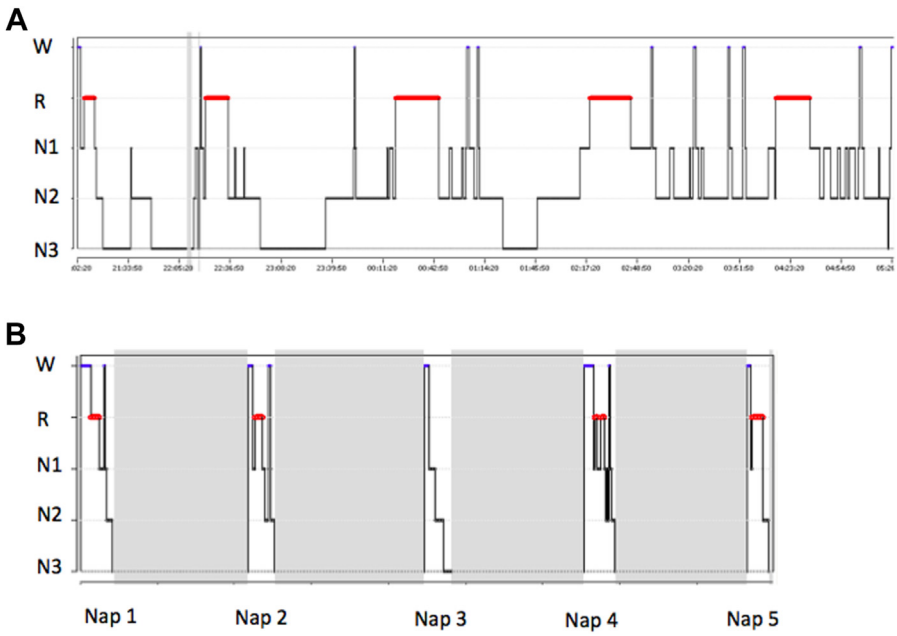

Fig. 2. Overnight PSG and MSLT of a patient with narcolepsy. (*A*) Overnight PSG shows a nocturnal sleep onset REM period (defined by REM sleep within 15 minutes of sleep onset, which is a biomarker for narcolepsy. Sensitivity is 55% and specificity is 97% in children aged 6–18 years with narcolepsy type 1 (Andlauer 2013, Reiter 2015). (*B*) MSLT includes a series of five 20-minute nap opportunities at 2-hour intervals.

type 2 and idiopathic hypersomnia.[34,106] For people with idiopathic hypersomnia, the sensitivity of the MSLT is low, and the test-re-test reliability is similarly poor.[94–96] For these individuals, alternative diagnostic testing or new biomarkers are needed.

Within the ICSD3, diagnosis of idiopathic hypersomnia is also possible with documentation of prolonged sleep duration on either extended PSG or actigraphy as an acceptable alternative to the MSLT criteria. Extended sleep duration is defined as 11 hours on both extended PSG (up to 24 hours) or as averaged over 7 days on actigraphy. There is data to suggest that long sleep time measured on extended PSG has superior sensitivity in idiopathic hypersomnia.[107] These 24 to 36-hour protocols provide improved diagnostic accuracy and reliability; however, they are rarely feasible in clinical sleep laboratories, not currently reimbursed, and not validated for pediatric idiopathic hypersomnia. Actigraphy uses motion to estimate sleep–wake patterns and has been studied in central disorders of hypersomnolence,[108,109] and although it has the advantage of measuring sleep wake in the home setting, it is not widely available due to cost and limited reimbursement. Of note, this diagnostic pathway is based only clinical actigraphs, not direct-to-consumer devices,[110] and has not been validated in children or adolescents.

Alternative Evaluation

In addition to neurophysiologic testing, for a select group of people with hypersomnolence and suspicion for narcolepsy type 1, CSF testing for orexin (hypocretin) level may be diagnostic. In children and adolescents with daytime sleepiness, low CSF orexin (hypocretin) level (<110 pg/mL) alone is sufficient for the diagnosis of narcolepsy type 1.[57] For example, CSF orexin (hypocretin) testing may be a useful alternative diagnostic pathway for a patient with clinical episodes consistent with cataplexy who is unable to undergo the MSLT, or unable to taper off of REM-altering medications in preparation for the MSLT. Orexin (hypocretin) levels are (by definition) greater than 110 pg/mL in narcolepsy type 2; if a patient with suspected narcolepsy type 2 has CSF testing with low orexin (hypocretin), the diagnosis changes to narcolepsy type 1. In children, sleepiness often precedes cataplexy, and the presence of low CSF orexin alone would be diagnostic for narcolepsy type 1; these children and adolescents can be counseled that they may develop cataplexy over time.

Serum human leukocyte antigen (HLA) testing can have some clinical utility. Narcolepsy type 1 has a strong association with HLA-DQ1B*06:02, which is present in 98% of people with narcolepsy type 1,[57,111] although this is also seen in up to 30%

of healthy sleepers[111] and is most useful when negative to exclude diagnosis. Because it is rare to see narcolepsy type 1 without this HLA positivity, CSF orexin (hypocretin) is very unlikely to be low and lumbar puncture would be of low yield. HLA-DQ1B*06:02 may be either present in 40% to 60% of people with narcolepsy type 2.[112,113]

Clinical scales have been validated for use in the assessment of symptom frequency, severity, and burden for pediatric narcolepsy (The Pediatric Narcolepsy Severity Scale[114] validated in children aged 10 years and older) and for idiopathic hypersomnia (the Idiopathic Hypersomnia Severity Scale[115] validated in adolescents and adults aged 16 years and older). Of note, these scales query symptoms beyond severity of daytime sleepiness, such as cataplexy, sleep paralysis, and sleep-related hallucinations in narcolepsy, and sleep inertia and daytime naps in idiopathic hypersomnia. Both of these severity scales show treatment sensitivity. Otherwise, other commonly used validated instruments for excessive daytime sleepiness used for pediatric outcome measurement include the ESS-CHAD[4] (Janssen 2017) and the PDSS.[5]

Disease Management

There are currently no cures for narcolepsy or idiopathic hypersomnia, and the therapeutic goals are to improve sleepiness and other burdensome symptoms to optimize academic/work, social, and familial functioning. For daytime sleepiness, there are both pharmacologic and behavioral approaches to lessen symptom severity. Medications selection should be individualized to the patient's risk/benefit ratio, cost, and potential adverse effects with existing comorbidities. Nonpharmacologic interventions including maintaining a regular sleep schedule, avoiding sedating daytime medications/substances, lifestyle adjustments, physical activity, and inclusion of academic accommodations are important for all children and adolescents with hypersomnolence. Scheduled daytime naps, 15 to 30 minutes duration, can temporarily improve excessive daytime sleepiness and improve alertness in children and adolescents with narcolepsy. Naps are typically less helpful for sleepiness mitigation in idiopathic hypersomnia because of difficulty waking from naps and sleep inertia. **Box 2** includes sample school accommodations for children and adolescents with narcolepsy and idiopathic hypersomnia.

Box 2
Helpful accommodations for children and adolescents with narcolepsy or idiopathic hypersomnia

Children

1. Consider a study period during the academic day. This allows patients to get more work done while medications are active and permits time for naps as needed.
2. Have patient sit at front of class to help with vigilance. Alternatively, some children prefer sitting in back of classroom so they can take a scheduled nap.
3. Schedule a 30-minute nap during the day in quiet, safe area in school. Patients typically benefit from this nap after lunch or early afternoon.
4. Allow patients to chew gum, drink cool water, and/or take movement breaks during class/test taking to maintain alertness.
5. Request extra time for completion of homework/tests/projects. Patients need to keep 9 to 10 hours for sleep at night and this can be difficult if they are overwhelmed by homework responsibility.
6. Maintain exercise daily as exercise.

Adolescents/College Students

1. Priority registration for high school/college courses so patients can schedule classes for when they are most alert.
2. Provision of class notes/audio recordings if patient is too sleepy to pay attention in class.
3. Private dorm room for undisturbed sleep at night.
4. A dorm room close to classes so patients can take scheduled naps.

Treatment of Pediatric Narcolepsy

For children and adolescents with narcolepsy, the only United States Food and Drug Administration (FDA) approved therapies are traditional stimulant medications (amphetamines, methylphenidate) for treatment of daytime sleepiness and sodium oxybate or lower sodium oxybate (calcium, magnesium, potassium, and sodium oxybates) for the treatment of excessive daytime sleepiness and cataplexy (7–17 years). Based on a meta-analysis of available pediatric clinical trials, the American Academy of Sleep Medicine issued clinical practice guidelines for the treatment of pediatric narcolepsy.[116] These guidelines issued conditional recommendations for the use of modafinil for the treatment of daytime sleepiness and sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy. The lack of clinical trials with sufficient number of participants and/or use of validated instruments limited the

Table 2
Treatments of narcolepsy and idiopathic hypersomnia in children and adolescents (excessive daytime sleepiness and cataplexy

Medication	Dose	Side Effects
Stimulants		
Methylphenidate immediate release Methylphenidate ER or SR Methylphenidate (concerta) Methylphenidate (patch) Dextroamphetamine IR Amphetamine/ dextroamphetamine IR Lisdexamfetamine	10–60 mg/d in 2–3 divided doses 20–60 mg/d 18–54 mg/d 10–30 mg/d 5–40 mg/d in 1–2 divided doses 10–40 mg/d in 1–2 divided doses 30–70 mg/d	Common: anorexia, poor growth or weight loss, sleep disturbance, jitteriness, tics, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects Monitor blood pressure, caution if family or personal history of cardiac arrhythmias
Wake-promoting medications		
Modafinil Armodafinil	50–200 mg in 1–2 divided doses 50–250 mg in 1–2 divided doses	Common: headache, nervousness, nausea, insomnia Rare, serious: severe rash (Stevens-Johnson syndrome), psychiatric events CYP3A4/5 induction: impair effectiveness of steroidal contraceptives Exposure during pregnancy increases risk of congenital malformations
Others		
Sodium oxybate, lower-sodium oxybate	2–9 g/night in 2 divided doses 20–30 kg: 6 g max 30–45 kg: 7.5 g max >45 kg: 9 g max	Common: morning sedation, nausea, weight loss, dizziness, enuresis, sleep walking, tremor, constipation, worsening of obstructive sleep apnea (OSA) Rare, serious: confusion, severe sedation, coma Not to be used with alcohol, sedatives, or hypnotics Central pharmacy with enrollment in REMS program
Atomoxetine	0.5–1.2 mg/kg/d in 1–2 divided doses (max, 100 mg/d)	Common: weight loss, abdominal pain, nausea, anorexia, headache Rare, serious: suicidal ideation, psychosis, mania, cardiovascular events, priapism, hepatotoxicity
Medication	**Dose**[a]	**Side Effects**
Sodium oxybate, lower-sodium oxybate	2–9 g/night in 2 divided doses 20–30 kg: 6 g max 30–45 kg: 7.5 g max >45 kg: 9 g max	Common: morning sedation, nausea, weight loss, dizziness, enuresis, sleep walking, tremor, constipation, worsening of OSA Rare, serious: confusion, severe sedation, coma Not to be used with alcohol, sedatives, or hypnotics

(*continued on next page*)

Table 2
(*continued*)

Medication	Dose[a]	Side Effects
Tricyclic antidepressants Clomipramine Imipramine Protriptyline	25–100 mg/d at bedtime 25–75 mg/d, 2 divided doses 5–10 mg/d in 1–2 divided doses	Common: dry mouth, constipation, diaphoresis, blurred vision, somnolence, weight gain, orthostatic hypotension Rare, serious: cardiotoxicity, suicidal ideation, bone marrow suppression, serotonin syndrome
Selective serotonin reuptake inhibitors Fluoxetine Sertraline Citalopram	10–30 mg/d 25–200 mg/d 10–40 mg/d	Common: nausea, insomnia, tremor Rare, serious: suicidal ideation, QT prolongation, serotonin syndrome
Serotonin norepinephrine reuptake inhibitors Venlafaxine	37.5–75 mg/d	Common: nausea, weight loss, dizziness, headache, constipation, insomnia, somnolence, tremor Rare, serious: suicidal ideation, QT prolongation, serotonin syndrome

[a] Doses for children aged 6 years and older, except clomipramine and protriptyline, which are for ages 10 and older.

ability to include recommendations for traditional stimulants and daytime naps for excessive daytime sleepiness treatment and SSRI/SNRI commonly used for cataplexy control. In clinical practice, stimulants are often the first-line therapy, based on US FDA approval. There are no longitudinal data regarding stimulant use in pediatric narcolepsy but clinical experience suggests children and adolescents can have short-term side effects including delayed sleep onset, reduced appetite, headaches, weight loss, and potential for worsening of comorbid conditions such as anxiety and depression. Long-term use seems safe in children with primary attention hyperactivity disorder with close follow-up but data have been inconsistent regarding the potential of stimulant growth effects.[117] Modafinil or armodafinil for excessive daytime sleepiness is typically second-line therapy if there is inadequate response or intolerance to stimulants. Although modafinil and armodafinil are not FDA-approved for patients under 18 years due to concerns of Stevens Johnson syndrome and psychosis, observational studies suggest significant symptomatic improvement of daytime sleepiness in pediatric narcolepsy and only minor side effects.[118–120] Use of sodium oxybate for pediatric narcolepsy has been the only medication studied in a randomized, placebo-controlled, clinical trial study,[121] and the study showed significant improvements in excessive daytime sleepiness and cataplexy from baseline with sodium oxybate use. There were rare adverse serious effects in this clinical trial including central sleep apnea, depression, and suicidality; more common side effects are listed in **Table 2**. Clinicians are required to enroll in a Risk Evaluation and Mitigation Strategies (REMS) program before receiving sodium oxybate. Lower-sodium oxybate was FDA-approved in 2020 for children aged 7 years and older and can be used with similar efficacy and tolerability as sodium oxybate. Lower-sodium oxybate could be considered if there is a concern about the high sodium content of sodium oxybate (about 1640 mg/d compared with 131 mg sodium at the maximal dose, 9 mg), such in cases of patients with elevated blood pressure or risk factors for hypertension.

Overall, given reports of increased cardiovascular disease in adults with narcolepsy,[122] close monitoring of blood pressure is recommended with narcolepsy treatments discussed. Newer treatments approved for adults with narcolepsy include solriamfetol and pitolisant. Pitolisant is a selective histamine 3 receptor antagonist/inverse agonist, and decreases cataplexy and sleepiness in adults,[123] although it is not yet been approved for children pending clinical trial data. A small case series suggests safety and improvement of daytime sleepiness and in children with Prader-Willi syndrome.[124] Solriamfetol, a selective

dopamine and norepinephrine reuptake inhibitor also improves sleepiness in adults with narcolepsy but has not been studied in children.[125,126] Orexin agonists are currently in clinical trial phases and may offer more effective therapies in the future.[127]

Commonly used medications for symptoms of daytime sleepiness and cataplexy, dosages, and associated side effects are summarized in **Table 2**.

Treatment of Pediatric Idiopathic Hypersomnia

There are no pharmacologic treatment options studied for pediatric idiopathic hypersomnia and no FDA-approved therapies. In adults, lower-sodium oxybate was recently approved for treatment of idiopathic hypersomnia based on a multicenter study of 154 adults aged 18-75 years (median age 39 years) showing improvement of excessive daytime sleepiness on the Epworth Sleepiness Score from the end of the stable dose period to the end of the double-blind, randomized, withdrawal period.[128] Additionally, lower-sodium oxybate was associated with benefits to overall idiopathic hypersomnia symptoms and patient impression of symptom severity relative to the placebo control.[128] The American Academy of Sleep Medicine clinical practice guidelines for the treatment of central disorders of hypersomnolence (published before this oxybate study) includes a recommendation for modafinil for the treatment of idiopathic hypersomnia in adults based on 1 randomized control trial and 3 observational studies.[116] There are less data to support the use of methylphenidate, pitolisant, or clarithromycin in adults with idiopathic hypersomnia.[116]

In clinical practice, clinicians typically treat the excessive daytime sleepiness in pediatric idiopathic hypersomnia with stimulants, modafinil, or armodafinil using similar guidance detailed in the narcolepsy section above. Similar accommodations as listed in **Box 2** can be applied for children and adolescents with idiopathic hypersomnia. Certainly, more study and clinical trial data are needed to guide pediatric practitioners in optimal pediatric idiopathic hypersomnia management.

SUMMARY

Narcolepsy and idiopathic hypersomnia have significant impact on optimal participation in school and social and family interactions. Obtaining a detailed clinical sleep history from children and adolescents and their caregivers is critical for early recognition of these disorders. Thoughtful interpretation of neurophysiologic testing is needed for accurate diagnosis of narcolepsy and idiopathic hypersomnia. Tailoring treatment approaches to meet the needs of individuals and account for medical and psychiatric comorbidities may also improve quality of life.

CLINICS CARE POINTS

- Narcolepsy is a lifelong disease that often presents in adolescence or childhood results in severe daytime sleepiness that impairs physical and mental health with impact on social, academic, and professional life.
- Daytime sleepiness in children may manifest as hyperactivity, irritability, or emotional lability.
- Children and adolescents with narcolepsy may experience symptoms of REM sleep intrusion into wake, such as sleep-related hallucinations, sleep paralysis, and cataplexy.
- Cataplexy is sudden loss of muscle tone triggered by strong, usually positive, emotion. In children, cataplexy presentation may be complex or atypical with dyskinesias or motor activity.
- Narcolepsy and idiopathic hypersomnia are often diagnosed with overnight PSG followed by MSLT. Insufficient sleep, circadian rhythm disorders, and certain medications may result is false-positive testing, and this study should be interpreted in the clinical context.
- Treatment of daytime sleepiness in narcolepsy or idiopathic hypersomnia may include sleep hygiene and scheduled naps but most people require pharmacotherapy. First-line treatments for sleepiness typically include stimulants, followed by modafinil/armodafinil. If both cataplexy and sleepiness are bothersome, sodium oxybate or lower-sodium oxybate may be first-line therapy.
- Mood should be monitored closely during treatment with medications that reduce cataplexy because there may be increased suicidal ideation with the initiation of antidepressants or oxybates.

DECLARATION OF INTERESTS

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SUPPLEMENTARY DATA

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