

EXPERT PERSPECTIVES

Sleeping Their Lives Away: Recognizing the Unique Burden of Idiopathic Hypersomnia in Your Patients

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This white paper will review the extensive burden associated with idiopathic hypersomnia (IH), spanning school, work, interpersonal relationships, and public health and safety. It includes important insights from IH experts who were convened to provide perspectives on the unique impact of IH on patients.

OVERVIEW OF IH

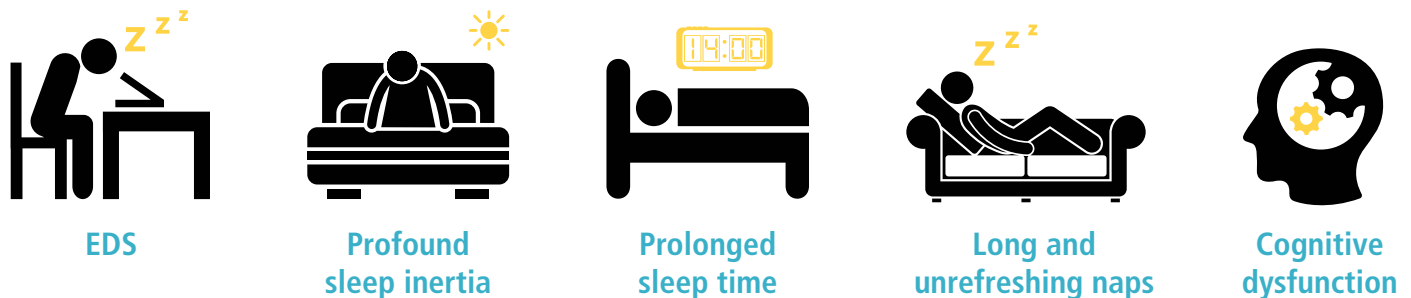
Idiopathic hypersomnia (IH) is a chronic neurological disorder that is characterized by nonrestorative sleep despite normal or longer than normal amounts of sleep each night.^{1,2} For these patients, quantity of sleep does not necessarily translate into a quality sleep.

“There’s something very unique about the capacity or the need to simply just keep the sleep system going almost indefinitely. Doctors need to recognize that pathologically long sleep is not OK. That’s something that’s just totally missed.”

– Robert Thomas, MD

Several symptoms are commonly observed in patients with IH, including excessive daytime sleepiness (EDS), profound sleep inertia, prolonged sleep time, prolonged and unrefreshing naps, and cognitive dysfunction (**Figure 1**).³

Fig 1. Symptoms commonly observed in patients with IH.³



EDS, excessive daytime sleepiness; IH, idiopathic hypersomnia.

Patients with IH remain sleepy regardless of how much time they spend asleep. As such, EDS is an essential feature of IH.^{3,4}

Additionally, severe and prolonged sleep inertia, characterized by prolonged difficulty waking up, repeated returns to sleep, irritability, automatic behavior, impaired motor function, and confusion, is often associated with IH.^{3,4} Some patients with IH have prolonged sleep time (typically, 12 to 14 hours per day), as well as long and unrefreshing naps.³ Furthermore, it has been reported that patients with IH are more likely to experience difficulties with concentrating and cognitive function than healthy control subjects.⁵

Although the clinical features of IH distinguish it from narcolepsy, obstructive sleep apnea, depression, and other disorders for which EDS is a key feature,^{2,3} diagnosis of IH may be challenging.^{2,6} This challenge in diagnosis is in part because EDS is a shared core feature of many disorders. Furthermore, there is no specific biomarker for IH.^{2,3} Patients may go undiagnosed for 10 to 15 years after the onset of their initial symptoms of IH.⁶

“These patients tend to sleep excessively, and they have lingering somnolence regardless of how much they’ve been able to sleep, which causes them to be impaired during the day.”

– Logan Schneider, MD

It is critical to consider that patients with IH may have several distinct symptoms of varying severity.¹ Even though symptoms do not manifest to the same degree for every patient, a tool has been developed to help assess symptoms associated with IH. The Idiopathic Hypersomnia Severity Scale is a tool to assess these symptoms, and it has established reliability for assessing and quantifying IH symptom severity, as well as detecting clinically significant changes following treatment and may be used to monitor patients with IH over time.⁷

IMPACT OF IH

Many patients with IH, even those with less severe symptomatology, experience various impairments to quality of life that extends to multiple domains.^{8,9} Patients may experience memory and attention problems, including feelings of one's mind going blank or making a mistake in a habitual activity. Patients often describe their difficulties with attention and cognition as "brain fog".^{2,5,6} Therefore, patients with IH may experience limitations in daily living activities, such as school, work, interpersonal relationships, and social activities.^{1,5,10,11} Severe sleepiness associated with disorders of hypersomnolence can cause accidents, posing a risk to public health and safety.^{12,13}

Academic and Career Performance

Patients with IH have difficulty fully waking from sleep without assistance⁹ and maintaining alertness in the morning, which, in turn, can lead to decreased work and academic performance.¹⁴ As in healthy controls, alertness of patients with IH may be dependent on external conditions, such as sunlight and indoor lighting. Dimly lit or dark rooms (i.e. lecture halls) can exacerbate feelings of drowsiness and induce sleep easily for patients with IH. Patients with IH report that they prefer to stand rather than sit, and prefer to walk while speaking. Therefore, sedentary work and some environments can be challenging for patient with IH, making it difficult to achieve vocational success.

The Hypersomnia Foundation, through an online patient registry launched in 2016, developed a questionnaire to assess symptoms in patients with IH. Results of this questionnaire indicated that brain fog, defined as "being unable to think clearly or concentrate at any time throughout the day," was the second most commonly endorsed symptom of IH, occurring in 83% of patients, following EDS, endorsed by 98% of patients (**Figure 2**).¹⁵ Some patients report improvement in brain fog with treatment of their IH symptoms. However, 54% of patients continue to report brain fog despite treatment. Notably, 84% of patients with IH report daily brain fog.

"This is not falling asleep when you don't want to. This sleep is pervasive. You are wearing it 24/7, not just having sleepiness here and there."

– David Rye, MD, PhD

"It seems to me the most disabling symptom separate from the fog all day long is just the ability to get where you need to be. The hardest thing patients have to do each day is wake up and get out of bed."

– David Rye, MD, PhD

Fig 2. Rates of "brain fog" in patients with IH as reported by a Hypersomnia Foundation patient registry questionnaire.¹⁵

In a questionnaire study for participants in the Hypersomnia Foundation patient registry

83% of participants with IH experienced brain fog daily



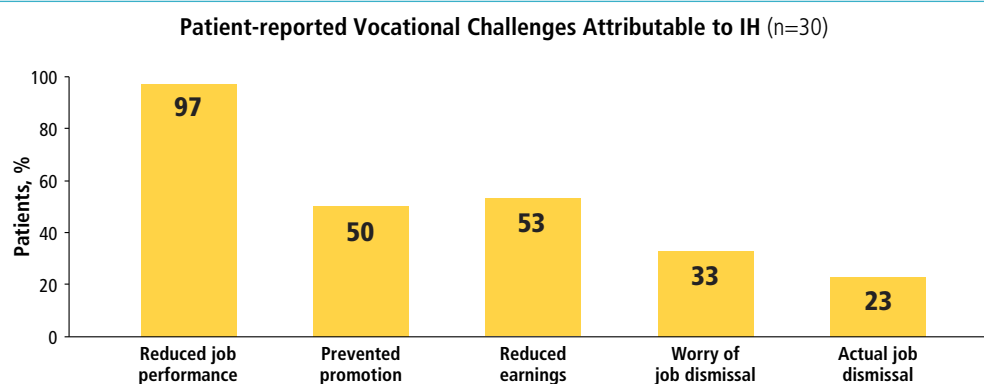
Among treated patients

54% experienced brain fog daily within the past 30 days
and
84% experienced brain fog daily when symptoms were at their worst

Additionally, IH has been associated with attention deficit hyperactivity disorder (ADHD). It has been hypothesized that ADHD symptoms may be consequences of EDS, or that they may be related to intrinsic features of a similar neurodevelopmental dysfunction. A cross-sectional study aimed to determine age at onset and relationship of EDS, inattention and hyperactivity–impulsivity symptoms in 2 clinical adult populations of drug-free patients with a primary diagnosis of ADHD (100 patients) or central hypersomnia (32 patients with NT1, 28 patients with NT2, and 40 patients with IH). Sixty-one percent of patients with hypersomnia had clinically significant ADHD symptoms, including 25% with a diagnosis of ADHD.¹⁶

In addition to problems maintaining alertness, patients with IH may also experience debilitating criticisms, such as arriving late to work and/or receiving negative comments from their employers, which, in some cases, may lead to being fired.¹⁷ In a questionnaire study of patients with IH (n=30) compared with sex- and age-matched healthy controls (n=30), patients with IH reported effects on several aspects of their life, including job performance, career success, and the risk of getting fired (**Figure 3**).¹³ These vocational effects may also lead to reduced earnings. In a population-based study of adults with hypersomnia disorders, 16.3% of participants with IH (N=129) reported currently being on disability.¹⁸ These problems may all contribute to the fact that patients with IH may take longer to attain their educational and professional goals.¹⁴

Fig 3. Job performance is often negatively impacted by IH.¹³



“Every patient who I’m supporting for short-term disability through the Family and Medical Leave Act is an IH patient.”

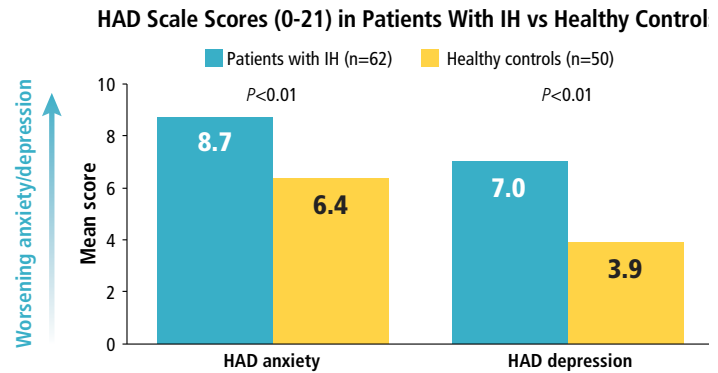
– Robert Thomas, MD

Psychosocial

The psychosocial impact of IH extends to personal relationships. In a study of 54 patients receiving treatment for their IH, 35% did not feel they received support from friends and family, and 13% had divorced or broken up with a partner because of their condition.¹⁰ Furthermore, parenting duties may be affected, as patients with IH may have difficulty waking up at night when their baby is crying or struggle to wake up in the morning to get children ready for school.¹

The mental health of patients with IH is also compromised, and many patients may experience anxiety or depression. In a population-based study of adults with hypersomnia disorders, participants with IH reported several mental health symptoms, including sad mood, lost interest, irritability, social isolation, concentration issues, anxiety, guilt/worthlessness, and worry. Referrals to mental health specialists were common in these patients.¹⁸ Additionally, in a controlled, prospective cohort of 62 patients with IH and 50 healthy patients, patients with IH expressed higher anxiety and depression scores on the hospital anxiety and depression rating scale (**Figure 4**).⁵

Fig 4. The mental health of patients with IH is negatively impacted.^{5,*}



HAD, Hospital Anxiety and Depression.

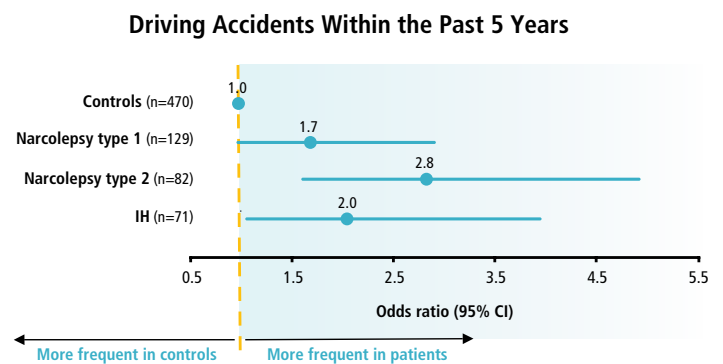
*Conducted using an in-person interview and a standardized questionnaire for all patients being monitored for 48 hours with suspected IH in a single hospital between 2005 and 2008.

“Patients with IH commonly report that their depression is driven by their severe fatigue and sleepiness and frustration with their inability to function at home, with friends and at work/school”
– Kiran Maski, MD, MPH

Public Health and Safety

The effects of IH can extend beyond impacts to the patient and their loved ones, as IH can have unexpected consequences for personal safety and public health. Drowsiness associated with IH may compromise certain abilities, such as driving, by reducing alertness or attentiveness.¹² A cross-sectional study of patients with IH compared with healthy controls reported that patients with hypersomnolence disorders have a significantly higher prevalence of driving accidents compared with healthy controls (**Figure 5**). In a separate questionnaire study, 47% of patients with IH reported household or occupational accidents and 17% of patients with IH reported accidents while smoking, whereas 0% of controls reported either of these types of accidents.

Fig 5. Patients with hypersomnolence disorders report significantly higher prevalence of driving accidents compared with healthy controls.^{12,*}



*Adjustment for gender, age, unmarried status, coffee intake, and energy drink consumption.

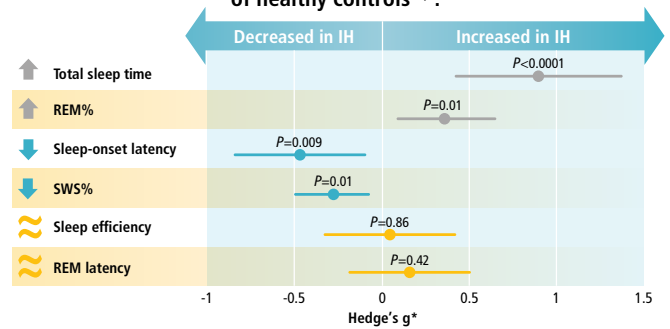
POTENTIAL ROLE OF NIGHTTIME SLEEP DYSFUNCTION IN IH

Emerging science suggests that nighttime sleep dysfunction may contribute to daytime sleepiness in IH.^{21,22} A systematic review and meta-analysis that included 10 studies found that, on average, several sleep architecture hallmarks distinguished patients with IH from healthy sleepers (**Figure 6**).²¹ Total sleep time and percent of rapid eye movement (REM) sleep were increased in patients with IH compared with controls, whereas time necessary to fall asleep and percent of slow-wave sleep were decreased in patients with IH compared with controls. Additionally, sleep efficiency and REM latency were similar between patients with IH and controls.

A separate study of deidentified sleep studies conducted at various sleep clinics in the United States between 2005 and 2015 found that patients with IH had high arousal indices, defined as number of arousals per hour, compared with controls.²² Arousal indices in patients with IH were similar in number to those of patients with narcolepsy type 1 and the authors of this study hypothesized that these high arousal indices may partially explain the nonrestorative sleep found in patients with IH.

Fig 6. Emerging science suggests that nighttime sleep dysfunction may be one contributor to the symptoms of IH.

In a meta-analysis of the nocturnal PSG sleep architecture of adult patients with IH, on average, several hallmarks differed from those of healthy controls^{21,*}:



*Based on a systematic review that included 10 studies, including nocturnal PSG data for IH and healthy controls. Meta-analysis compared standardized mean differences (Hedge's g) for total sleep time, sleep-onset latency, sleep efficiency, REM sleep percentage, SWS (slow-wave sleep or deep sleep) percentage, and REM latency. Moderator analyses were also conducted for variables with heterogeneity among studies (sleep onset latency, sleep efficiency, total sleep time).

"If your sleep is dysfunctional, you're going to experience these downstream symptoms, like long sleep and sleep inertia. This is a disorder that has these features."

– Robert Thomas, MD

LIMITATIONS OF TREATMENT FOR IH

IH is a distinct medical condition with a unique impact on patients, and it requires its own management considerations to address this impact. Current IH management is typically composed of both behavioral and pharmacological strategies.^{4,6,18,19} To date, the main goal of management strategies for IH has been to reduce daytime sleepiness,^{4,6,18} but these strategies may not address all of the effects of IH on patients. Components of management include good sleep hygiene, such as scheduled nocturnal sleep; behavioral modification, including counseling and psychotherapy or diet and exercise strategies; and, lastly, pharmacotherapy, which may include treatment with traditional stimulants, nonstimulant wake-promoting agents, and GABA_B agonists.^{4,6,18,19} Stimulants and wake-promoting agents are not FDA-approved to treat idiopathic hypersomnia.^{4,20}

Off-label treatments include those known to alleviate sleepiness associated with other disorders, but data on the efficacy of these treatments for IH are limited.²⁰ In an internet survey of 129 patients who self-identified as having IH (N=129), medication effectiveness was rated only a 5.4 out of 10.¹⁸ Additionally, patients may need to be on 2 or more medications to help control symptoms of IH.¹⁰ The Hypersomnia Foundation registry data show that treated patients (most commonly with psychostimulants) still have substantial rates of residual symptoms.¹⁵

Current management strategies that address EDS may not address the nonrestorative nature of sleep in IH, and optimal symptom management, including managing the burden of IH on patient lives, may not be achieved with current management approaches.^{2,4,6,18}

“We need to sort out the pathophysiology that we’re targeting here, and we may find those people that have some sort of sleep issue that is amenable to improving.”

—Logan Schneider, MD

CONCLUSIONS

IH is a unique medical disorder with characteristic symptoms that are distinguishable from other disorders like narcolepsy and obstructive sleep apnea.^{2,3,17,23} Changes in sleep architecture have been observed in patients with IH,^{21,2} and although patients with IH have characteristic sleepiness, the burden of IH extends far beyond sleepiness to impact academic and vocational performance, psychosocial domains, and public health and safety.^{8,9} Current therapies have limited patient-reported efficacy in IH.¹⁸ As such, there is a large unmet need in managing this condition. New therapeutic strategies that reduce both symptoms of IH and the burden associated with the condition are necessary to improve quality of life in patients with IH.

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