

Understanding the Multiple Symptoms of Idiopathic Hypersomnia, A Unique Sleep Disorder

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This white paper reviews the multiple symptoms that manifest in patients living with idiopathic hypersomnia. It includes important insights from experts on idiopathic hypersomnia who convened to provide perspectives on the role of these symptoms in diagnosis of the condition, the impact of these symptoms on patients in their daily lives, and the importance of managing all symptoms that a patient experiences.

Core Symptoms of Idiopathic Hypersomnia

Idiopathic hypersomnia is a rare and underrecognized sleep disorder characterized by heterogeneous symptoms that impact patients throughout the 24-hour cycle.^{1,2} Patients living with idiopathic hypersomnia are consumed by sleep, day and night.^{3,4} They often struggle to wake up and tend to not feel rested or refreshed when they do, even after a full night's sleep.^{1,2}

Idiopathic hypersomnia is characterized by multiple symptoms and has specific diagnostic criteria used to distinguish it from other disorders (**Figure 1**).³

“Patients with idiopathic hypersomnia may have high sleep efficiency, which implies good sleep, but in fact that sleep is of low efficacy, meaning it’s nonrestorative. Our job is to treat sleep to improve wakefulness.”

– Logan Schneider, MD

Figure 1: *International Classification of Sleep Disorders - Third Edition (ICSD-3)* Diagnostic Criteria and Supportive Clinical Features of Idiopathic Hypersomnia

ICSD-3 Diagnostic Criteria	Additional Supportive Clinical Features Include
<ul style="list-style-type: none"> • Excessive daytime sleepiness (EDS) ≥ 3 months • Absence of cataplexy • < 2 SOREMPs* • Presence of at least 1 of the following: <ul style="list-style-type: none"> - MSL ≤ 8 minutes on MSLT - Total 24-hour sleep time ≥ 11 hours on either 24-hour PSG or wrist actigraphy[†] • Insufficient sleep syndrome is ruled out • Hypersomnolence and/or MSLT findings are not better explained by other causes 	<ul style="list-style-type: none"> • Severe and prolonged sleep inertia • High sleep efficiency ($> 90\%$) • Long, unrefreshing naps (> 1 hour)

MSL, mean sleep latency; MSLT, multiple sleep latency test; PSG, polysomnography; SOREMP, sleep-onset rapid eye movement period.
*Or no SOREMPs if REM latency on preceding PSG is ≤ 15 minutes.
[†]In association with a sleep log averaged over at least 7 days.

The *International Classification of Sleep Disorders - Third Edition (ICSD-3)* diagnostic criteria and supportive clinical features include the core symptoms of idiopathic hypersomnia, which are the focus of this review. While excessive daytime sleepiness (EDS) is present in all patients with idiopathic hypersomnia,^{3,4} patients often experience other core symptoms, such as sleep inertia; long, unrefreshing naps; long sleep time; and cognitive impairment.^{3,5}

Additional symptoms commonly associated with idiopathic hypersomnia include high sleep efficiency, automatic behaviors, autonomic dysfunction, and depressive symptoms.^{3,5-8} This expert panel has identified the core and associated symptoms critical to the differential diagnosis of idiopathic hypersomnia (**Figure 2**); while these differentiating symptoms are not necessarily specific to idiopathic hypersomnia, in the context of the full clinical presentation, they may help differentiate idiopathic hypersomnia from other conditions. Additionally, understanding the constellation of key symptoms of idiopathic hypersomnia may aid in its recognition by limiting misdiagnoses due to symptoms being mistaken for other conditions.³

“It’s important to establish chronic EDS as a component of diagnosis, but several other disorders present with EDS, so we must look to the differentiating symptoms of idiopathic hypersomnia.”

– Haramandeep Singh, MD

Figure 2: Differentiating Symptoms of Idiopathic Hypersomnia Include Select Core and Associated Symptoms

Core Symptoms		Associated Symptoms	
Nondifferentiating Symptoms	Differentiating Symptoms		Nondifferentiating Symptoms
EDS	Sleep inertia	High sleep efficiency	Autonomic dysfunction
Cognitive impairment	Unrefreshing naps		Automatic behaviors
	Long sleep time		Depressive symptoms

“This is not just a condition of sleepiness, like we all may experience after getting a bad night of sleep. There’s a whole long list of other symptoms that these patients experience.”

– Shane Drahos, MD

Excessive Daytime Sleepiness

EDS is the most common symptom of idiopathic hypersomnia, and is a symptom required by *ICSD-3* diagnostic criteria.^{3,9} EDS is the inability to stay awake or alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep.^{3,4} Patients may describe EDS as the continuous urge to sleep.¹

TO ASSESS FOR EDS, IT IS IMPORTANT TO ASK PATIENTS QUESTIONS SUCH AS, “DURING THE DAY, WHILE CARRYING OUT ACTIVITIES THAT ARE NOT VERY STIMULATING, DO YOU EVER STRUGGLE TO STAY AWAKE?”¹⁰

Most patients living with idiopathic hypersomnia never feel fully awake.¹ They may rely on multitasking and other multimodal arousal strategies to maintain their alertness. Decrements in daytime alertness can challenge individuals’ ability to excel at school, work and generate income, participate in recreational activities, and achieve socially optimal outcomes in their personal and professional lives. Additionally, adequate alertness is a key prerequisite to safe driving, and sleepiness is known to increase risk for driving accidents.¹¹ Driving accidents are associated with higher subjective sleepiness measures, and patients living with idiopathic hypersomnia report more driving accidents and near misses within the prior 5 years than do controls (**Figure 3**).^{11,12}

“In narcolepsy, people have trouble staying awake, but in idiopathic hypersomnia, people have trouble waking up. They’re sleepy in both conditions, but they’re sleepy for different reasons.”

– Thomas Scammell, MD

“A few years ago, I started to feel tired almost all the time. I started feeling really embarrassed that I couldn’t stay awake. My grades were slipping, and I was trying to hide it. I was concerned that being so sleepy would hold me back.”

– Anonymous person living with idiopathic hypersomnia

Figure 3: Patients With Idiopathic Hypersomnia Report Higher Prevalence of Driving Accidents Compared With Healthy Controls^{12,*}

In a cross-sectional study, patients with idiopathic hypersomnia (n=56) had a

2.04 × 95% CI, 1.05-3.95[†]

increased risk for driving accidents within the past 5 years compared with healthy controls (n=404)

*In a cross-sectional study of patients with central disorders of hypersomnolence classified based on their primary *ICSD-3* diagnosis. Data were collected from a national research program on narcolepsy and other central disorders of hypersomnolence performed in French reference centers for rare hypersomnia diseases between 2008 and 2011. Healthy subjects were recruited via advertisement from the general population.

[†]Adjusted for gender, age, unmarried status, coffee intake, and energy drink consumption.

“We need to consider safety in these patients who are excessively sleepy. We need to assess whether their symptoms cause them to be unsafe. One person might leave the stove on and fall asleep. Another may have difficulty driving without falling asleep.”

– Nathaniel Watson, MD, MSc

Because EDS can be associated with many different conditions, it is important to assess for other symptoms to determine the cause of EDS.³

Profound Sleep Inertia

Sleep inertia is prolonged difficulty waking up with repeated returns to sleep.³ This trouble transitioning from sleep to wake may last for several hours and may include disorientation, irritability, poor coordination, and automatic behavior (performing of tasks without control or without remembering). Patients may describe profound sleep inertia as “sleep drunkenness” or prolonged grogginess or confusion when waking up. Waking up and getting out of bed may feel impossible.¹ Sleep inertia is frequently present in patients with idiopathic hypersomnia and may be more prominent than EDS.¹¹ **This expert panel considers sleep inertia the cornerstone of idiopathic hypersomnia**, that in their clinical practices is found in about 90% of patients with the disorder, and notes that it may be experienced when waking from nighttime sleep or following naps.

Severe and prolonged sleep inertia is included as a supportive clinical feature in the *ICSD-3* diagnostic criteria for idiopathic hypersomnia,³ and this symptom is more commonly reported in idiopathic hypersomnia than other sleep disorders, including narcolepsy, making it a particularly important distinguishing feature to help identify patients with idiopathic hypersomnia.¹³

“When discussing sleep inertia, I simply ask patients, ‘What’s it like when you wake up in the morning?’ It’s important to understand the difference between having a little bit of difficulty waking up in the morning, which many of us may experience from time to time, versus this profound difficulty that we’re talking about with this particular disease.”

– Nathaniel Watson, MD, MSc

“Waking up on time with idiopathic hypersomnia is very tricky. Some days I will be in almost a coma-like sleep where it is just impossible to arouse me, whereas other days I will hear my alarm. I have a system where a friend will start to call me if I do not let them know that I am awake. Some days it has taken upwards of 40 phone calls along with my alarms going off to wake me up. I also have people who will run over to the house if the phone calls are not working.”

– Meghan, person living with idiopathic hypersomnia

SOME QUESTIONS THAT MAY AID IN ASSESSING THE FREQUENCY, DURATION, AND INTENSITY OF SLEEP INERTIA INCLUDE¹⁰

1. HOW FREQUENTLY IS IT DIFFICULT FOR YOU TO WAKE UP IN THE MORNING WITHOUT SEVERAL ALARMS OR THE HELP OF SOMEONE CLOSE?
2. AFTER A NIGHT'S SLEEP, HOW LONG DOES IT TAKE YOU TO FEEL YOU ARE FUNCTIONING PROPERLY AFTER YOU GET UP?
3. IN THE MINUTES AFTER WAKING UP, DO YOU EVER DO IRRATIONAL THINGS AND/OR SAY IRRATIONAL THINGS, AND/OR ARE YOU VERY CLUMSY?

“Sleep inertia is the cornerstone of idiopathic hypersomnia, and all other symptoms fall in line after that. I’ve had patients complain it takes a long time to wake up, and as a result, they’ll fight off taking naps because they know they will have difficulty waking up.”

– Shane Drahos, MD

Sleep inertia can constitute a very important problem that interferes with the demands of school start times and day-shift employment. Patients with sleep inertia may use multiple alarm clocks or may try other interventions, such as utilizing loud voices along with somatic stimulation to wake up. These interventions to aid in waking up may cause individuals to depend on others, strain interpersonal relationships, and even pose safety risks.¹¹

“When it comes to advocating for our patients, we need to understand that sleep drunkenness and safety go hand in hand. We need to assess how this is putting these patients at risk. This is not just grogginess in the morning. It is profound.”

– Logan Schneider, MD

“Safety is really important. I recently had a mom who was really worried that she was not waking up or that she was walking around in this sleep-drunken state and could not fully care for her children.”

– Phyllis Zee, MD, PhD

Long, Unrefreshing Naps

Patients with idiopathic hypersomnia often experience long (>1 hour), unrefreshing naps.³ They may describe not feeling better or rested after a nap, and they may even feel worse. Because of this, some people with idiopathic hypersomnia may avoid napping or fight the urge to nap because it does not help them feel better and it is hard to predict how long they will sleep. Of those who do nap during the day, the majority report taking naps longer than 1 hour.¹

“When you have a patient come into your office and complain that they’re exhausted all day, you ask them, ‘How many naps do you take throughout the day?’ They’ll usually say, ‘I would never nap because I feel worse.’ That’s something that stands out clinically when we’re looking at these patients.”

– Shane Drahos, MD

“I can nap anywhere. I’m still never truly awake afterwards, and I’m always thinking about the next opportunity that I’ll be able to go to sleep.”

– Anonymous person living with idiopathic hypersomnia

“I had a patient tell me that he felt like he was playing roulette with his day if he took a nap because he didn’t know how long he would stay asleep or how long he would feel really sleepy after he woke up.”

– Shane Drahos, MD

Long, unrefreshing naps are included as a supportive clinical feature of idiopathic hypersomnia in the *ICSD-3* criteria.³ Additionally, this symptom is viewed as a clinical characteristic that may help to distinguish between idiopathic hypersomnia and narcolepsy when either of these diagnoses is suspected. Patients with idiopathic hypersomnia often find naps to be long and unrefreshing in nature, while patients with narcolepsy generally find short naps to be refreshing. Hence, patients with narcolepsy tend to have more frequent intentional napping compared with patients with idiopathic hypersomnia, who usually do not benefit from prescribed or scheduled naps as part of their treatment.^{3,13}

TO CHARACTERIZE THE TYPES OF NAPS PATIENTS MAY EXPERIENCE, IT IS IMPORTANT TO ASK PATIENTS¹⁰

- 1. WHAT IS YOUR IDEAL NAP LENGTH?**
- 2. HOW DO YOU GENERALLY FEEL AFTER YOU HAVE TAKEN A NAP?**

Long Sleep Time

Long sleep time is the ability to sleep for many hours, often for 11 hours or more in a 24-hour period, during both the night and day. At least 30% of patients living with idiopathic hypersomnia have prolonged sleep time (typically, 12 to 14 hours in a 24-hour period). While long sleep time is not a requirement for diagnosis of idiopathic hypersomnia, patients must either have a total 24-hour sleep time of at least 11 hours (on either a 24-hour polysomnography or wrist actigraphy) or mean sleep latency (MSL) ≤ 8 minutes on the multiple sleep latency test (MSLT) to meet the *ICSD-3* criteria.³

Long sleep time may also be present in individuals with other conditions, such as long-sleeper syndrome, so these conditions are important to exclude when assessing a patient for idiopathic hypersomnia. However, in contrast to patients with idiopathic hypersomnia, those with long-sleeper syndrome, feel refreshed and do not have daytime sleepiness and difficulty awakening if they are allowed to sleep as long as they need.³

“When we think about long sleep, we need to consider not just sleep at night but also sleep during the day. It is important to consider that long sleep of at least 11 hours may span across the full 24 hours of the day. I ask my patients, ‘How long can you sleep?’ That’s distinguishing. People with idiopathic hypersomnia will say, ‘I can sleep all day.’”

– Phyllis Zee, MD, PhD

“Long sleep can occur after a period of insufficient sleep, so we must also follow up with the question ‘Can you sleep that long every day?’”

– Thomas Scammell, MD

TO ASSESS FOR LONG SLEEP TIME, IT IS IMPORTANT TO ASK PATIENTS, “WHAT IS YOUR IDEAL DURATION OF NIGHTTIME SLEEP (ON THE WEEKEND OR A HOLIDAY, FOR EXAMPLE)?”¹⁰

“I need 12 hours of sleep to function. But I can really sleep as long as you give me.”

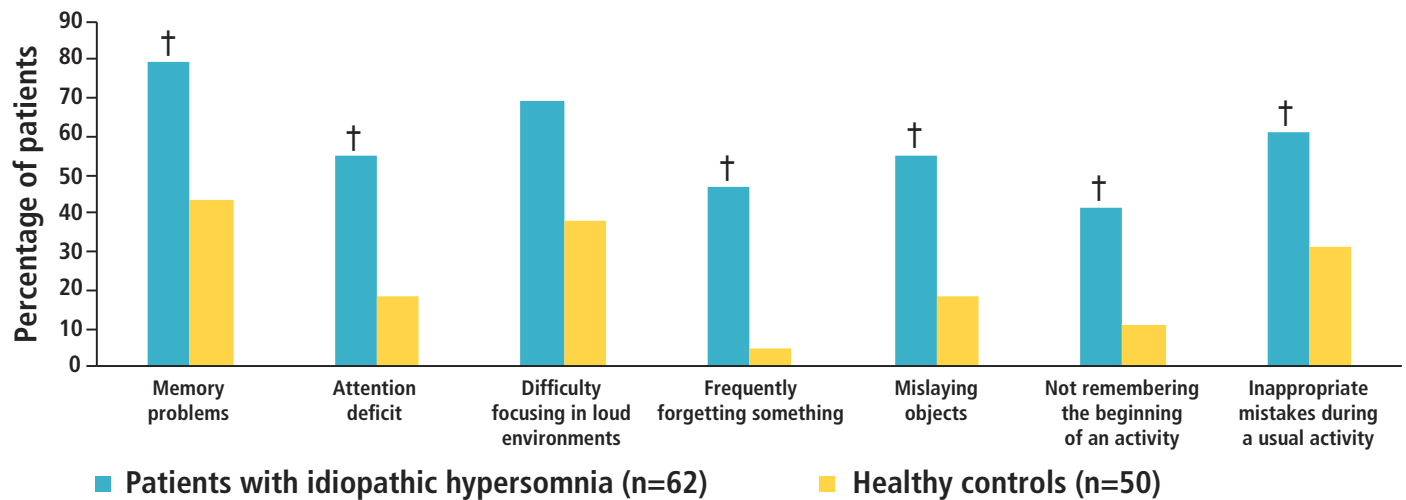
– Anonymous person living with idiopathic hypersomnia

Cognitive Impairment

Patients living with idiopathic hypersomnia often experience difficulty focusing, trouble thinking clearly, or memory problems due to EDS.⁵ Patients often describe these symptoms as “brain fog.”⁹

Patients with idiopathic hypersomnia have been found to have higher rates of various cognitive problems compared with healthy controls, based on an interview study (Figure 4).⁵

Figure 4: Patients With Idiopathic Hypersomnia Report Higher Rates of Cognitive Problems Compared With Healthy Controls*



*In a study conducted between 2005 and 2008 of 62 patients with idiopathic hypersomnia and 50 healthy controls matched by age and sex. Subjects participated in face-to-face interviews and completed a large, systematic questionnaire. All patients with suspected idiopathic hypersomnia and 30 of the control subjects underwent a 48-hour sleep-wake monitoring procedure.
† $P < 0.01$.

While cognitive impairment is not specific to idiopathic hypersomnia and does not necessarily help with differential diagnosis, it is a common complaint that may affect the daily functioning of patients living with idiopathic hypersomnia,¹¹ so it is important to consider as a key component of managing the symptoms of idiopathic hypersomnia.

PATIENTS SHOULD BE ASKED, “DO YOU CONSIDER THAT YOUR EXCESSIVE DAYTIME SLEEPINESS IS A PROBLEM IN TERMS OF YOUR PROPER INTELLECTUAL FUNCTIONING (EG, PROBLEMS WITH CONCENTRATION, MEMORY PROBLEMS, DECREASE IN YOUR INTELLECTUAL PERFORMANCE)?”¹⁰

“Cognitive dysfunction is not specific to idiopathic hypersomnia, but it is something that has a big impact on the daily lives of these patients.”

– Phyllis Zee, MD, PhD

“My brain feels foggy and it is hard to think or remember. When a task is difficult, I feel like I will never be able to complete it on time.”

– William, person living with idiopathic hypersomnia

“I know living with idiopathic hypersomnia is more than just being sleepy. There are all of the cognitive connections. And for me, those are some of the most challenging things.”

– Beth, person living with idiopathic hypersomnia

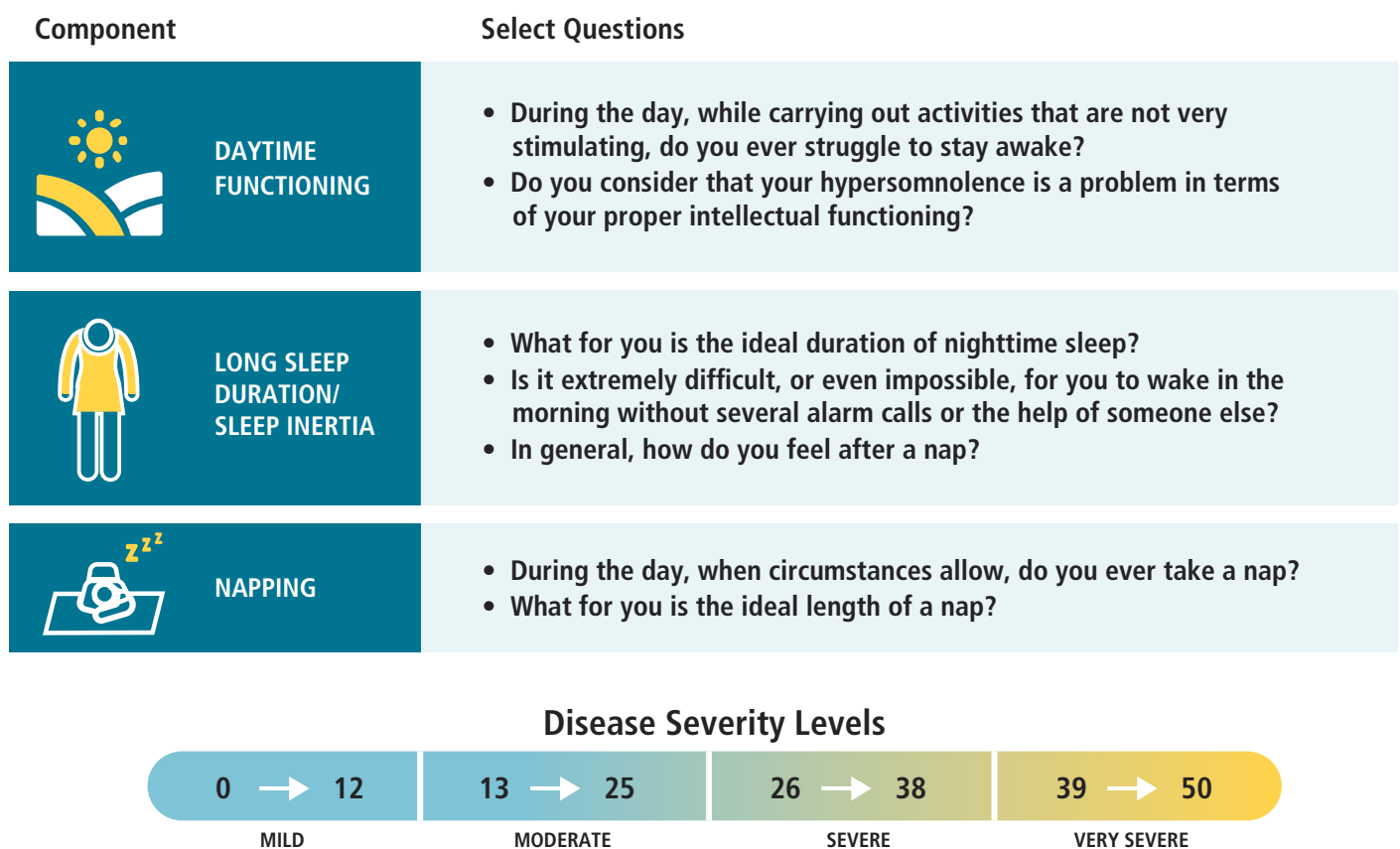
Tools to Assess Symptoms of Idiopathic Hypersomnia

Currently available tools may aid in assessing the severity of symptoms associated with idiopathic hypersomnia. For example, the Epworth Sleepiness Scale (ESS) is a patient-reported questionnaire designed to measure sleep propensity in a simple, standardized way. This questionnaire consists of 8 questions, and ESS scores greater than 16 out of 24 indicate a high level of daytime sleepiness. The ESS can be used to measure levels of EDS in patients suffering from EDS due to a number of conditions.¹⁴

A newer scale, the Idiopathic Hypersomnia Severity Scale (IHSS), is a validated questionnaire geared toward assessing the severity and impact of the symptoms of idiopathic hypersomnia (**Figure 5**).¹⁵

IHSS questions were developed based on the key symptoms of idiopathic hypersomnia and their consequences, and this 14-question survey assesses 3 main components of idiopathic hypersomnia: 1) daytime functioning, 2) long sleep duration/sleep inertia, and 3) napping.¹⁶ Items are scored from 0 to 3 or 4 to provide a total score ranging from 0 to 50, with higher scores indicating more severe and frequent symptoms. It has been found that a cutoff score of 22/50 discriminates patients with untreated idiopathic hypersomnia from controls without EDS.¹⁵ Additionally, further validation has shown that a difference of 4 points has been estimated to be the minimum clinically important difference. For this reason, the IHSS can be used to track symptoms of idiopathic hypersomnia over time and may be useful to assess patient response to treatment.¹⁶

Figure 5: Components and Disease Severity Levels of the Idiopathic Hypersomnia Severity Scale



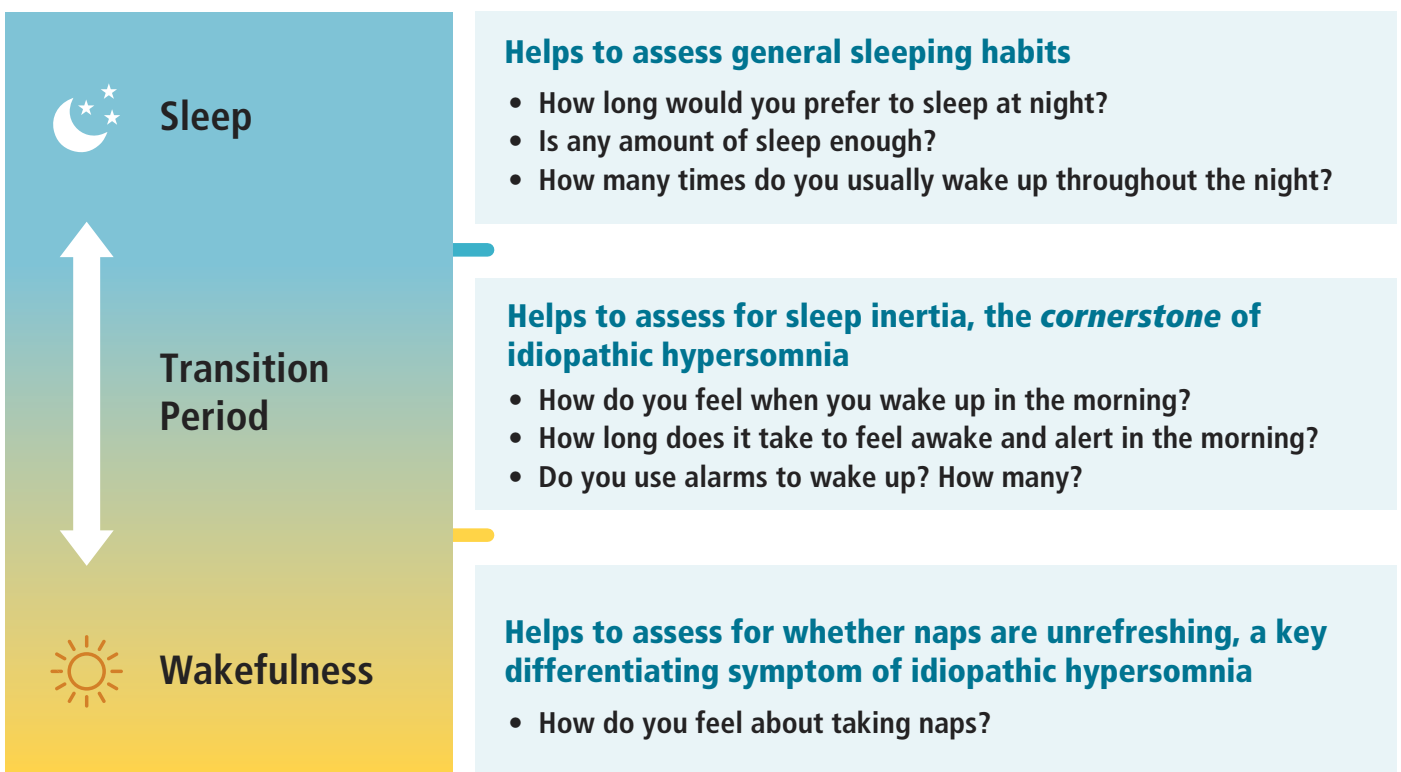
“In the IHSS, we get at different aspects of the symptoms. For instance, we ask 3 questions related to sleep inertia, assessing the frequency, the duration, and the intensity of sleep inertia. When screening, it helps to quantify the severity of the condition. The answer cannot just be yes or no, but there needs to be a grading to quantify the symptoms.”

– Yves Dauvilliers, MD, PhD

Conclusion

Idiopathic hypersomnia is a unique sleep disorder with multiple symptoms, including EDS and the *cornerstone* symptom of sleep inertia, which need to be recognized and managed.¹¹ To improve recognition of idiopathic hypersomnia, it is crucial to assess for all of its core and associated symptoms. There are several specific features to look for and ask about related to each symptom, but when a patient presents with EDS, this expert panel recommends initiating the clinical conversation by using a series of open-ended, nonleading questions to assess for the presence or absence of all symptoms (**Figure 6**). If suspicion of one or more of these symptoms is identified, then more specific questions related to the frequency, duration, and intensity of these symptoms should be asked. This assessment, along with results of sleep testing, may help to strengthen the confidence in the diagnosis. The IHSS is a separate validated tool that can be used both to assess for severity of symptoms and to help track response to treatment over time.^{15,16}

Figure 6: Recommended Open-Ended Questions to Ask Patients Who Present With EDS to Assess for Symptoms of Idiopathic Hypersomnia



Current widely used management strategies focus on reducing daytime sleepiness in patients living with idiopathic hypersomnia, but patients using these therapies continue to report daily symptoms, including EDS, difficulty awakening (sleep inertia), and cognitive symptoms.⁹

“We often see that symptoms continue to impact patients with idiopathic hypersomnia, despite treatments that they are on.”

– Phyllis Zee, MD, PhD

“When discussing treatment options for idiopathic hypersomnia, I write out the core symptoms that the patient is experiencing and explain that we may need to explore a treatment option that can help address their main complaints.”

– Shane Drahos, MD

“Our job is to do more than just help with the sleepiness patients experience. For patients with idiopathic hypersomnia, if half of their day every day is spent sleeping, they have 50% less or 25% less in a day than the average person. This has a huge impact on their life. This impact is why we should be treating this whole condition, not just keeping the patient awake.”

– Logan Schneider, MD

To provide comprehensive care for people living with idiopathic hypersomnia, all symptoms should be considered as a part of determining an appropriate treatment plan.

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