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Idiopathic Hypersomnia

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Abstract

Idiopathic hypersomnia (IH) is a chronic neurological disorder that results in daytime sleepiness, frequently accompanied by long nocturnal or daytime sleep, unrefreshing sleep, difficulty in awakening, cognitive dysfunction, and autonomic symptoms. The cause of idiopathic hypersomnia is presently unknown, although a genetic predisposition is suggested by the strong family history of similar symptoms. Dysfunction of autonomic, inflammatory, or immune systems has been proposed, and patients with IH have been found to have an endogenous modulator of GABA-A receptors within their cerebrospinal fluid. Diagnosis of IH involves a careful clinical history, with particular attention to the possibility of other disorders with similar symptomatology, and objective testing with actigraphy, polysomnography, and multiple sleep latency testing. There are no FDA-approved treatments for IH symptoms, which are typically treated with off-label use of medications approved for narcolepsy. Modafinil is first line and supported by two randomized, controlled trials in IH patients. A substantial fraction of IH patients are refractory or intolerant to standard treatments, and different treatment strategies, employing novel therapeutics, are necessary in these cases. Even with current treatment options, quality of life and safety may remain impaired in patients with this challenging chronic disease.

Keywords

Idiopathic hypersomnia; narcolepsy; excessive daytime sleepiness; multiple sleep latency test; sleep drunkenness

Introduction

Idiopathic hypersomnia (IH) is a chronic neurologic disorder that manifests as pathologic daytime sleepiness with or without prolonged sleep durations. Population-based estimates of the frequency of IH are difficult to obtain, given the requirements for electrophysiologic testing and ruling out of other disorders that may cause similar symptoms. Clinic-based estimates of IH prevalence are limited by differing referral patterns and biases, such that estimates of the relative frequency of IH to narcolepsy with cataplexy vary substantially, anywhere from 1:10 to greater than 1:1 (1–5). As such, the true prevalence of IH is

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unknown. Using a questionnaire-based algorithm, Ohayon et al have demonstrated that the symptom of excessive sleepiness, associated with irresistible daytime naps, multiple naps in the same day, non-restorative nocturnal sleep of at least 9 hours, or difficulty waking after sleep, is present in 0.5% of the population (6). While presumably not all of these individuals would meet diagnostic criteria for idiopathic hypersomnia, it is clear that the symptoms of IH are not uncommon.

As the name “idiopathic” hypersomnia implies, the pathophysiology of IH is presently unknown. Hypocretin deficiency, known to cause narcolepsy type 1, is not present in patients with IH (7). Cerebrospinal fluid from patients with IH, and several other central disorders of hypersomnolence, has been shown to enhance activity at GABA-A receptors in vitro, in excess of that of cerebrospinal fluid from controls (8). Although this enhancement of GABAergic transmission has not been shown to be causal to sleepiness or long sleep durations in patients with IH, biological plausibility is demonstrated by the known GABAergic mechanisms of sleep onset and maintenance, as well as the prominent role of GABA-A receptor agonists/modulators in the production of pharmacologic sleep and anesthesia (9–12). Further, symptoms of IH are reversible in some patients with use of GABA-receptor antagonists or negative allosteric modulators (see **Treatment Resistance**, below) (8, 13, 14).

Family history of excessive sleepiness, IH, or another central disorder of hypersomnolence is seen in 34–38% of IH patients (4, 15, 16), with parent-child transmission suggested by the finding that 12.5% of IH patients have at least one parent who routinely sleeps more than 9.5 hours per night (17). Taken together, these reports suggest a genetic contribution to IH. However, the strong association between narcolepsy type 1 and HLA DQB1*0602 is not observed in patients with IH, in whom the rate of positivity for this allele ranges from 8–27%, depending on the population, and approximates the rate in controls (4, 18–20). An immune system dysregulation, unique from that implicated in narcolepsy type 1, might be present in patients with IH, as suggested by their significantly increased rates of comorbid inflammatory or allergic disorders (17, 21) and altered IgG profile compared to controls (22). Disruption of autonomic nervous system functioning, with a shift toward increased vagal tone, has been noted in patients with IH compared to controls, possibly contributing to some of the vegetative symptoms (faintness, orthostatic hypotension, Raynaud’s syndrome) that are commonly observed in IH patients (17, 23, 24).

Classically, sleep efficiency is greater than 90% in patients with IH (4, 16, 18, 24, 25), although some studies have reported mean values in the high 80s (15, 19). The tendency for high sleep efficiency is somewhat at odds with the recently-proposed hypothesis that patients with IH have fragmented sleep, as evidenced by more sleep stage changes, more N1 sleep, and more awakenings per hour than either controls or patients with narcolepsy type 1 (26). Abnormalities in slow wave sleep percentage have been proposed but inconsistently observed (1, 4, 16, 18, 19, 25, 26). A single, small study has suggested an increase in spindle activity in IH patients compared to those with narcolepsy (type unspecified) (27).

Patient Evaluation Overview

Core diagnostic features of IH

Daytime sleepiness, defined as an irresistible need to sleep or episode of daytime sleep, is the core diagnostic feature of idiopathic hypersomnia. Current diagnostic criteria in the International Classification of Sleep Disorders (ICSD), third edition (24), require a combination of sleepiness for least three months, not better explained by another disorder or substance, and specific polysomnographic or actigraphic criteria (see Box 1).

Ancillary symptoms of IH

Several ancillary features are commonly seen in people with IH:

1. Long sleep duration

Earlier editions of the ICSD explicitly defined a subset of idiopathic hypersomnia defined by long sleep times (i.e., > 10 hours for the main sleep period). Although current criteria do not distinguish those with long sleep from those without, long sleep times can be used to confirm an IH diagnosis (24).

2. Prolonged and unrefreshing naps

Similar to long sleep at night, naps during the day tend to be of long duration in patients with IH (4, 15, 24). Patients with IH often find naps to be unrefreshing (4, 15–18, 24). The clinical consequence of this is that, unlike in patients with narcolepsy type 1, patients with IH often do not benefit from prescribed or scheduled naps as part of their management.

3. Sleep inertia/sleep drunkenness

Patients with IH often demonstrate prolonged and pronounced difficulty with awakening from nocturnal sleep and daytime naps. This symptom is sometimes referred to as “sleep drunkenness”, to distinguish it from the milder and physiologic state of sleep inertia seen even in healthy controls (28). Sleep drunkenness occurs in nearly half of IH patients (28, 29) and presents a clinical challenge because patients may have difficulty awakening enough to take their wake-promoting medications. Dosing of stimulant medications one hour before planned awakening (which often requires assistance from a family member), or even dosing of stimulants at bedtime, may be necessary to overcome this symptom (28, 30). While not yet tested in a controlled fashion, melatonin at bedtime has been advocated for use in IH patients with sleep drunkenness (18, 31); this has had mixed results in our clinical experience but is a relatively low-risk intervention.

4. “Brain fog”/cognitive dysfunction

Subjective reports from patients with IH suggest that cognitive dysfunction is frequently present. Memory problems are reported by 79% of IH patients and attention problems by 55%. A feeling of one’s mind going blank (58%)

or making a mistake in a habitual activity (61%) are also reported commonly by IH patients, more so than by controls for all of these symptoms (17). A small study suggests that cognitive symptoms in patients with IH may be sufficiently pronounced that 1 in 5 patients also meets criteria for attention-deficit disorder (32).

Diagnostic testing for IH

The diagnosis of IH rests heavily on objective monitoring of sleep time and “sleepability” (i.e., the speed with which people fall asleep when attempting to do so, on multiple sleep latency testing (MSLT)) (Box 1). Previous versions of the ICSD have required an MSLT mean sleep latency of less than 8 minutes for the diagnosis of IH (33). However, data have shown that it is common for patients with clinical diagnoses of IH to demonstrate mean sleep latencies longer than this 8 minute threshold (4, 18), including 71% of those with long sleep times (18). Therefore, current ICSD criteria for IH also include an objectively measured sleep time of at least 660 minutes (by 24 hour polysomnography or averaged across at least one week of actigraphy), which can be used to confirm an IH diagnosis in patients with a mean sleep latency greater than 8 minutes (24). Whether or not the current criteria fully capture the spectrum of IH remains to be determined. Indeed, the ICSD-3 notes that there may be patients who meet all criteria for IH except the objective documentation criterion (i.e., not meeting MSLT, 24 hour PSG, or actigraphy criteria), and that these patients may still be clinically considered to have IH, especially if other causes of symptoms have been comprehensively excluded (24). Although this situation is reported to be rare by the ICSD-3, a prospective series of consecutive patients with a clinical diagnosis of IH found 29% (30/105) to have neither a mean sleep latency less than 8 minutes nor at least 660 minutes of sleep during 24 hour monitoring (18). In 100 consecutive patients evaluated for EDS, in whom psychiatric diagnoses, medication effects, insufficient sleep duration, and other sleep disorders had been carefully excluded, 33% had mean sleep latency > 8 minutes; in 24 hour ad lib PSG of these 33 patients, mean sleep time was less than 500 minutes (19), suggesting that many of these patients would remain excluded from a diagnosis under current criteria. Yet, those who did not meet IH diagnostic criteria were indistinguishable from those who did meet criteria on all measured sleep variables (19).

Differential diagnosis of IH

Because sleepiness is a core feature of multiple disorders, because there is currently no validated biomarker that is diagnostic of IH, and because ancillary symptoms of IH can be seen in other disorders, the differential diagnosis of IH can be challenging. In some cases, e.g., the differentiation between IH and insufficient sleep syndrome, careful attention to history and diagnostic testing can convincingly distinguish these disorders. In other cases, a diagnosis is rendered based on phenomenology and best clinical judgement, but important unanswered questions remain about pathophysiologic overlap. Differential diagnostic considerations include:

1. Insufficient sleep syndrome versus IH

Insufficient sleep duration can result in daytime sleepiness that mimics the sleepiness reported by patients with IH and that results in MSLT findings consistent with IH. However, the combination of clinical history, sleep logs, and actigraphic monitoring generally allows this diagnosis to be ruled in or out with a reasonable degree of certainty. Patients reporting sleepiness who are found to have insufficient sleep durations should be advised to extend sleep times to at least 8 hours, and then reassessed for resolution of sleepiness after several weeks on the new schedule.

2. The narcolepsies (type 1 and type 2) versus IH

Clinical features of IH and narcolepsy type 1 (NT1) are fairly distinct: patients with IH do not have cataplexy, while patients with NT1 do; patients with IH have high sleep efficiency with few nocturnal awakenings, while patients with NT1 have fragmented nocturnal sleep; patients with IH have long and unrefreshing naps, while patients with NT1 generally find short naps to be restorative.

In contrast, the distinction between IH and NT2 can be considerably more difficult. Cataplexy is absent in both disorders. Other components of the “narcolepsy tetrad”, *i.e.*, sleep paralysis and sleep-related hallucinations, are commonly seen in patients with NT2 but their presence in approximately one quarter of IH patients prevents them from being useful features to rule out a diagnosis of IH (see Table 1). Long sleep times may be present in NT2 (34). Sleep drunkenness, while relatively understudied in NT2 versus IH, appears to be about as common in both disorders (28). Fragmented nocturnal sleep, while common in NT1, is no more common in NT2 patients than in IH patients (limited to those NT2 who were HLA DQB1*0602 negative in one study) (1, 25, 35). In cluster analysis (*i.e.*, independent of pre-existing assumptions about diagnosis), symptoms and MSLT findings combined result in three clear clusters: a cluster of those with NT1, a cluster of those with IH and long sleep times, and a cluster containing both those with NT2 and IH without long sleep times (36).

As a result of this symptom overlap, the differentiation between IH and NT2 rests entirely on the presence or absence of at least two sleep-onset REM periods (SOREMs) on PSG/MSLT (with 0–1 SOREMs in patients with IH). In light of this, the limitations of the MSLT on this measure are particularly important. Test-retest reliability of multiple SOREMs in patients reporting problematic daytime sleepiness in the absence of cataplexy is relatively poor, with 31% of patients changing across the threshold of 2+ SOREMs between two MSLTs (37). This finding is mirrored in the general population, in which the finding of multiple SOREMs has a kappa of only 0.1, *i.e.*, repeatability is only minimally higher than expected by chance alone (38). At present, it is unknown if IH and NT2 are truly separate disorders, if they are the same disorder but appear distinct because of limitations of MSLT measurement, or if they may reflect a common pathophysiology occurring in people with different underlying REM-sleep propensity.

3. Delayed sleep phase syndrome versus IH

In patients with delayed sleep phase syndrome, preferred circadian timing for sleep is later than what is optimal for functioning in society, e.g., a person who will tend to sleep from 3 am until 11 am if able to do so absent external forces but must awaken for work at 8 am. As a result of the misalignment between preferred circadian timing and external obligations, patients with DSPS are frequently sleep deprived and have substantial daytime sleepiness.

The difficulty in distinguishing IH from DSPS springs from several key issues. First, patients with DSPS will frequently present with the combination of daytime sleepiness and sleep drunkenness, i.e., a combination of symptoms classically seen in people with IH. In patients with DSPS, the etiology of sleep drunkenness is presumed to be the combination of chronic sleep deprivation (making it difficult to awaken because of increased homeostatic sleep pressure) and the circadian misalignment (making it difficult to awaken because the circadian drive is to sleep at the time of attempted awakening). Second, patients with IH are known to have a tendency toward a delayed sleep phase (18) and the presence of an evening chronotype in patients with IH increases their likelihood of displaying sleep drunkenness (17). Recent work has shown that the amplitude of circadian clock gene expression over the circadian period is decreased in skin fibroblasts from IH patients compared to controls (39) and that patients with central disorders of hypersomnolence (including IH) are more likely than controls to have a polymorphism in circadian gene *CRY1* (40), adding support to the hypothesis of altered circadian function as a key component of IH pathophysiology or symptomatology. Thus, the presence of sleep drunkenness cannot rule out DSPS and the presence of a delayed sleep schedule cannot rule out IH.

Sleepiness in patients with DSPS is thought to result from chronic sleep deprivation caused by attempting to function in a world that is out of alignment with the preferred phase. This implies that patients with DSPS who are allowed to sleep a sufficient duration of hours should have improvement in daytime sleepiness. As such, history, sleep logs, and actigraphy with ad lib sleep are very important in distinguishing these two disorders. A patient who cannot fall asleep until 3 am and who is sleepy when sleeping from 3–8 am but whose sleepiness resolves when allowed to sleep from 3–11 am likely has DSPS alone, while a patient who routinely sleeps from 3 am until 11 am and is sleepy despite this may have both IH and a tendency toward a delayed sleep phase.

4. Hypersomnia associated with a psychiatric disorder versus IH

One of the most challenging differential diagnostic considerations in IH is the entity of hypersomnia associated with a psychiatric disorder. Although the ICSD-3 explicitly refrains from assigning causality in the diagnosis, noting that hypersomnia "associated with" a psychiatric disorder may be more correct than hypersomnia "due to" a psychiatric disorder, criteria still require a judgement about whether the main diagnosis is IH (in which psychiatric disease may be comorbid) or whether it is primarily psychiatric. Both sets of criteria require the

exclusion of the other disorder (41). Current criteria suggest that this distinction may revolve around sleep quality and mean sleep latency test results (24), although the specificity of these findings based on existing data has been questioned (42).

5. Hypersomnia due to a medical disorder versus IH

Certain medical and neurologic disorders are known to result in daytime sleepiness. Two well characterized examples are Parkinson's disease and myotonic dystrophy (43, 44). In many cases, the comorbid medical disorder has already been diagnosed when a patient presents with excessive sleepiness, and the diagnosis of hypersomnia due to a medical disorder is made relatively easily. However, in some cases, sleepiness may present prior to the apparent onset of the other disorder, such that an index of suspicion for incident medical disorders should be maintained in patients with IH. This lag between onset of sleepiness and onset of other symptoms of a medical disorder is perhaps best described in patients with Parkinson's disease, in whom sleepiness is known to predict the subsequent onset of the movement disorder 4–12 years later (45–47).

Other medical conditions are also implicated in causing sleepiness, with varying levels of evidence. Our routine laboratory screen (in addition to a comprehensive history) for such disorders in patients being evaluated for IH includes a complete blood count, full iron panel (iron, total iron binding capacity, % saturation, and ferritin), B12, thyroid stimulating hormone (with additional thyroid testing if this results in the high-normal or high range), and free and total carnitine.

Although the treatment of some of medical conditions associated with hypersomnolence will result in improvement in sleepiness, it is important to keep in mind that this is not always the case. For example, treatment of Parkinson's disease patients with dopamine agonists may worsen, rather than lessen, daytime sleepiness (48, 49). In these cases, management of sleepiness may be an important, but separate, clinical goal.

See table 2 for a summary of clinical features in IH and these disorders with similar symptoms.

Non-pharmacologic Treatment Options

Quality of life and daytime functioning can be profoundly affected in patients with IH, even following treatment (50–52). Although the distinction between IH with mood dysfunction and hypersomnia associated with a psychiatric disorder can be challenging (41), symptoms of depression are commonly encountered in people with IH and may add to the burden of disease (52). In light of these factors, increasing attention has recently been paid to the possible role of non-pharmacologic therapy as adjunct treatment in patients with IH (52). The vast majority of IH patients (96.1%) endorse using at least one non-pharmacologic strategy for management of their illness (52). The most commonly used non-pharmacologic strategies include caffeine (endorsed by 82.2% of IH patients), daytime naps (81.4%), and scheduling of nocturnal sleep (75.2%). Yet, the effectiveness of non-pharmacologic

strategies for IH, on a 1–10 scale where ten is most effective, is universally rated as poor. Most effective were caffeine (only 3.3 $\pm$ 2.6 out of 10), nicotine (3.2 $\pm$ 2.9 out of 10), and scheduled nocturnal sleep (3.0 $\pm$ 2.3 out of 10); daytime naps, exercise, diet, temperature manipulations, chewing gum, mindfulness, and yoga all received numerically lower scores (52). Patients with IH reported nearly all interventions as less effective than did patients with narcolepsy in the same study.

Safety counseling is an important non-pharmacologic aspect of the clinical care of patients with IH, just as it is in patients with narcolepsy (53). Such counseling revolves around two key issues: 1) medication side effects or interactions; and 2) driving and other safety-critical activities. Routine treatment of IH patients raises several potential medication concerns. First, amphetamines carry “black box” warnings regarding their potential for abuse, dependence, drug diversion, and cardiovascular side effects. Second, modafinil and armodafinil may interfere with effectiveness of hormonal birth control. Patients with central disorders of hypersomnolence, including IH, also have an increased risk of motor vehicle accidents (54) and treatment may not fully abolish this risk (55). Other safety-critical tasks (e.g., use of heavy machinery, power tools, etc.) may be compromised in some patients. Performance on maintenance of wakefulness testing (MWT) predicts on-road driving performance in patients with IH and narcolepsy (55, 56), and may be useful to guide decision-making, when available.

As with other chronic diseases, support groups and patient advocacy groups may be beneficial. Education regarding the availability of local, national, and online resources (e.g., the Hypersomnia Foundation, hypersomniafoundation.org) should be part of patient counseling when appropriate.

Spontaneous remission of IH has been reported to occur in approximately 20% of cases in which this measure is reported (See Table 4), but factors that predict such remission remain incompletely defined.

Pharmacologic Treatment Options

There are currently no medications approved by the United States Food and Drug Administration (FDA) specifically for the treatment of idiopathic hypersomnia and, until relatively recently, there were no published, randomized controlled trials (RCTs) of any treatment for IH. The most recent practice parameter from the American Academy of Sleep Medicine, which was published in 2007 prior to the publication of the first three RCTs of IH, recommended modafinil as an option for the treatment of IH (57), based on an open-label clinical series showing reduction in drowsiness and sleep attacks in 15 IH patients (58). Other medications recommended in this practice parameter, based on their beneficial effects on sleepiness in patients with narcolepsy but absence of data in patients with IH, were amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (57). Clinical series of IH patients treated with these medications are found in Table 3.

The first RCT to include patients with IH was published in 2014 (55). This crossover trial compared modafinil (400 mg, divided into two doses) and placebo on the ability to maintain

wakefulness on MWT and driving performance on an on-road driving test. Fourteen patients with IH were included in the total sample of 27 patients. Use of modafinil significantly decreased inappropriate line crossings on the driving test, i.e., improved driving safety, compared to placebo, but did not normalize performance to that of controls. Similarly, modafinil improved ability to maintain wakefulness on MWT but treated patients remained significantly sleepier than controls (55).

In an parallel-group RCT including 33 IH patients (without long sleep time per ICSD-2 criteria), modafinil (200 mg, divided into two doses) decreased subjective sleepiness measured with Epworth Sleepiness Scale scores compared to placebo. Differences in MWT between modafinil and placebo were not significant, although the modafinil group had significant improvements in maintenance of wakefulness compared to their own baseline (59).

Treatment Resistance

Clinical series of IH patients reveal that many patients do well with monotherapy, but approximately ¼ of patients have treatment-resistant symptoms despite use of standard therapies. In a series of 85 IH patients (by ICSD-2 criteria), 58% required only one treatment for their symptoms, and 65% of patients were ultimately able to achieve complete control of symptoms (15). An additional 26% had partial relief of symptoms, with 9% demonstrating a poor response. In another series, using somewhat less stringent diagnostic criteria, 18/25 patients (72%) demonstrated satisfactory symptom control with unspecified stimulant use (16). Among 54 patients meeting ICSD-2 criteria other than MSLT mean sleep latency, 32 (61%) were considered responders to mono- or combined therapy (4). Considering only modafinil, response rates of 83% (n = 18) (58) and 89.3% (for at least moderate improvement, n = 75) (60) have been reported. In an internet survey of 129 patients self-reporting a diagnosis of IH, medication effectiveness was rated only 5.4 out of 10 (+/- 1.9, where 10 is most effective), significantly lower than effectiveness rated by patients with narcolepsy in the same survey (52). Across the entire hypersomnolent group (i.e., people with either type of narcolepsy or IH), medication side effects prevented consistent use of pharmacotherapy for EDS in 23% of patients (52).

In cases with treatment-refractory sleepiness or intolerance to standard treatments, alternate pharmacologic strategies are needed. A number of different classes of medications have been proposed for the treatment of IH, including: GABA-A receptor antagonists/negative modulators (clarithromycin and flumazenil), GABA-B/gamma hydroxybutyrate receptor agonists, histamine H3 inverse agonists, levothyroxine, non-amphetamine stimulants, and transcranial direct stimulation (see Table 5 for details). Of these interventions, only clarithromycin has been evaluated in an RCT including patients with IH (13). In this study, clarithromycin 500 mg taken with breakfast and lunch resulted in a significant improvement in Epworth Sleepiness Scale scores and other subjective measures of IH symptoms, but did not improve psychomotor vigilance (13).

Summary

IH causes severe daytime sleepiness and impairs quality of life. Currently available medications insufficiently control symptoms in a substantial proportion of patients. Although recent work has provided clinicians with some direction in terms of pharmacologic and non-pharmacologic strategies, much work remains to be done. In particular, a clear knowledge of IH pathophysiology has the potential to open new avenues for the targeted, and more effective, treatments that are urgently needed.

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BOX 1**Idiopathic Hypersomnia Diagnostic Criteria, International Classification of Sleep Disorders, third edition (24)**

All of the following criteria must be met:

- 1** Daily daytime sleepiness, defined as an “irrepressible need to sleep” or daytime sleep, that has been present at least 3 months
- 2** No cataplexy
- 3** No MSLT evidence for narcolepsy (i.e., fewer than two sleep onset REM periods on the overnight PSG and daytime MSLT considered together)
- 4** Electrophysiologic evidence of hypersomnolence, defined as either (or both) of:
 - a.** Mean sleep latency on MSLT of 8 minutes
 - b.** At least 11 hours of sleep per 24 hours, documented on a single 24 hour PSG or averaged across at least seven days of actigraphic monitoring during ad lib sleep
- 5** Insufficient sleep is ruled out (including immediately prior to 24 hour PSG, if performed)
- 6** No other disorder or substance use better explains the symptoms

Abbreviations: MSLT = multiple sleep latency test; REM = rapid eye movement; PSG = polysomnogram

Key Points

- Idiopathic hypersomnia is thought to be a rare disorder, but population-based estimates of prevalence are limited. Symptoms of idiopathic hypersomnia are not uncommon.
- Diagnosis of idiopathic hypersomnia requires the consideration of multiple other conditions that may better explain symptoms, such as insufficient sleep time, circadian rhythm disorders (especially delayed sleep phase syndrome), narcolepsy without cataplexy, hypersomnolence associated with psychiatric disease, and hypersomnolence due to medical conditions.
- Current diagnostic schema for IH diagnosis are imperfect, such that some patients do not meet criteria but still have problematic sleepiness.
- First line treatment for IH is generally modafinil (or the longer half-life armodafinil), which is supported by two randomized, controlled trials (RCTs) showing efficacy. Psychostimulants are often used for IH treatment, although data supporting their use are sparse.
- Medication-refractory symptoms or medication intolerance prevents control of symptoms in 1/4 of IH patients. In such cases, several alternate treatment options are available, of which clarithromycin has been shown in a small RCT to improve symptoms.

Table 1

Features of the “narcolepsy tetrad” in patients with IH

Feature	Frequency in IH patients
Daytime sleepiness	100% (by definition)
Cataplexy	0% (by definition)
Sleep paralysis *	
• Bassetti 1997 (16)	17/42 (40%)
• Anderson 2007 (4)	3/77 (4%)
• Ali 2009 (15)	7/69 (10%)
• Sasai 2009 (5)	13/59 (22%)
• Vernet 2009 (18)	21/75 (28%)
• Sasai-Sakuma 2015 (25)	114/395 (29%)
• SLEEP PARALYSIS TOTAL	175/717 (24%)
Sleep-related hallucinations *	
• Bassetti 1997 (16)	18/42 (43%)
• Anderson 2007 (4)	4/77 (5%)
• Ali 2009 (15)	3/66 (4%)
• Sasai 2009 (5)	15/59 (25%)
• Vernet 2009 (18)	18/75 (24%)
• Sasai-Sakuma 2015 (25)	129/395 (33%)
• HALLUCINATIONS TOTAL	187/714 (26%)

* In series where only a percentage affected was reported (rather than the number affected), the number of affected patients was calculated assuming the total number of IH patients was used to generate the percentage (i.e., could not account for the possibility of missing data).

Table 2

Clinical features and differential diagnosis of Idiopathic Hypersomnia

	IH	NT2	ISS	DSPS	Psychiatric	Medical
Sleepiness	Present	Present	Present	Present	Present	Present
Long sleep times	Frequently	May be present	Absent by definition	Absent if allowed to habitually sleep at preferred schedule (24)	May be present, although distinction between time asleep and time in bed may be important (61)	May be present
Sleep inertia	Frequently present	Frequently present (based on small series)	Limited data	Commonly present	Commonly present (62–64)	Limited data
Depressive or other mood symptoms	May be present	May be present	May be present as a consequence of chronic short sleep (24)	May be present (24)	Present by definition	May be present (e.g., Parkinson's disease)
Mean sleep latency on MSLT	< 8 minutes by definition (if MSLT criteria are used for diagnosis)	< 8 minutes by definition	May be decreased (24); short sleep increases likelihood of MSL < 8 minutes with 2+ SOREMs (38)	Limited data: sleep latencies may increase over the course of the day (65)	< 8 minutes in 25% of patient with psychiatric hypersomnolence (42)	PD: wide-ranging estimates for MSL across studies; 20–24% of PD patients unselected for sleepiness have MSL < 8 min (66) MD: wide-ranging estimates across studies; 13–92% have MSL < 8 min (generally higher in those reporting EDS) (67)
Sleep onset REM periods on PSG/MSLT	0–1 by definition	2 or more by definition	2 or more may occur (24); short sleep increases likelihood of mean sleep latency < 8 minutes with 2+ SOREMs (38)	Limited data	Appear to be rare; 2+ SOREMs reported in 2/25 patients with bipolar and hypersomnolence; other studies have reported no SOREMs in patients with psychiatric hypersomnia (42)	PD: Up to 1/3 rd of sleepy PD patients have 2+ SOREMs (66) MD: 2+ SOREMs in 33–60% of sleepy MD patients and 25–35% of MD patients unselected for EDS (67)

Abbreviations: DSPS = delayed sleep phase syndrome, EDS = excessive daytime sleepiness, IH = idiopathic hypersomnia, ISS = insufficient sleep syndrome, MD = myotonic dystrophy, Medical = hypersomnolence due to a medical disorder, MSLT = multiple sleep latency test, MSL = mean sleep latency, NT2 = narcolepsy type 2, PD = Parkinson's disease, PSG = polysomnography, Psychiatric = hypersomnolence associated with a psychiatric disorder. SOREM = sleep-onset REM period

Table 3

Modafinil and traditional psychostimulants for IH treatment: Case series *

	Sample size with IH	Response rate	Duration of follow up
Modafinil			
• Lavault 2011 (60)	N = 104 prescribed modafinil (monotherapy in 96.1%); mean max dose 318 mg +/- 192 mg	-major to moderate improvement in 67/75 patients with CGI data available	4.0 +/- 5.0 years
• Ali 2009 (15)	N = 50 prescribed modafinil; mean daily dose 367.4 mg +/- 140.9	-25/50 remained on modafinil at EOM -18/25 complete symptom relief	Median 2.4 yrs (4.7 IQR)
• Anderson 2007 (4)	N = 54 initially prescribed modafinil; mean daily dose 400 mg (range 100–1000 mg)	-39/54 remained on modafinil monotherapy -24/39 responders	3.8 +/- 2.1 years
Bastuji 1988 (58)	N = 18 prescribed modafinil monotherapy; dose range 200–500 mg/day	-83% improved; 11% lost to follow up; 6% discontinued for side effects	2 months
• MODAFINIL TOTAL	N = 226	-124/197 (63%) remained on modafinil with good response	
Methylphenidate			
• Ali 2009 (15)	N = 61 prescribed methylphenidate; mean daily dose 50.9 mg +/- 27.3 mg	-40/61 remained on methylphenidate at EOM -25/40 complete symptom relief -41% remained on methylphenidate with complete response	Median 2.4 yrs (4.7 IQR)
Amphetamine-dextroamphetamine			
• Ali 2009 (15)	N = 8 prescribed amphetamine-dextroamphetamine; mean daily dose 79.3 mg +/- 30.6 mg **	-4/8 remained on amphetamine-dextroamphetamine at EOM -2/4 complete response -25% remained on amphetamine-dextroamphetamine with complete response	Median 2.4 yrs (4.7 IQR)
Dextroamphetamine			
• Ali 2009 (15)	N = 7 prescribed dextroamphetamine; mean daily dose 35.7 mg +/- 44.4 mg	-2/7 remained on dextroamphetamine monotherapy, both poor responders	Median 2.4 yrs (4.7 IQR)
• Anderson 2007 (4)	N = 8 prescribed dextroamphetamine monotherapy; mean daily dose 30 mg	-5/8 responders	3.8 +/- 2.1 years
• DEXTROAMPHETAMINE TOTAL	N = 15	-5/15 (33%) responded to dextroamphetamine	

* None of these medications are approved for use in idiopathic hypersomnia by the US FDA.

** Maximum FDA recommended dose for amphetamine-dextroamphetamine for use in narcolepsy is 60 mg/day.

Abbreviations: CGI = clinical global impression; EOM = end of monitoring; IQR = interquartile range

Table 4

Spontaneous remission rates in IH

Study	Sample size	Remission rate	Time period
Kim 2016 (68)	24	32.5%	5.5 years after diagnosis
Anderson 2007 (4)	77	14%	Followed at least one year
Bassetti 1997 (16)	35	25.7%	Followed at least one year
TOTAL	136	20.3%	

Table 5

Treatment options for treatment-refractory IH*

Class and Medications	Dosage	Level of evidence for use in IH	Availability	Side effects/other considerations
GABA-A receptor antagonists/negative modulators				
• Clarithromycin (13, 69)	500 mg with breakfast and lunch; up to 1000 mg bid in some cases	One cross-over RCT showing improvement in subjective sleepiness versus placebo; included 10 IH patients (of 20 total subjects); Clinical series of treatment-refractory patients (25 IH patients of 53 total) showed benefit in 64%, with 38% of patients continuing therapy	Widespread	Antibiotic resistance, superinfection, taste perversion, GI symptoms
• Flumazenil (14)	Transdermal cream or sublingual lozenges	Clinical series of treatment-refractory patients (36 IH patients of 153 total) demonstrated benefit in 63%, with 39% continuing therapy	Must be compounded; limited	Long term effects not fully known; seizures and arrhythmias known to occur with intravenous use
GABA-B/gamma-hydroxybutyrate agonists				
• Sodium oxybate (70)	Titrated up to 4.5 gm twice nightly (separated by 2.5 to 4 hours); mean dose in IH patients 4.3 gm/night; lower than in patients with NT1	Clinical series of treatment-refractory patients (comparing 46 IH patients to 47 patients with NT1) demonstrated mean ESS decrease of 3.5 +/- 4.5 points, but with 53% drop out rate	Within United States, must be dispensed by centralized pharmacy under FDA REMS program	Black box warnings for central nervous system depression, respiratory depression, and abuse. Drug diversion possibility (sodium salt of gamma-hydroxybutyrate)
Histaminergic				
• Pitolisant (71)	5–50 mg per day, taken once in the morning	Clinical series of treatment-refractory patients (including 65 IH patients of 78 total) demonstrating 36% responder rate and 37% continuing therapy	Not available in United States for any indication; European Medical Agency authorization for use in narcolepsy	GI symptoms, weight gain, insomnia, headache seen in > 10% of hypersomnia patients
Miscellaneous				
• Mazindol, a non-amphetamine stimulant (72)	1–6 mg/day, average 3.6 +/- 1.2 mg	Clinical series of treatment-refractory patients (including 37 IH patients of 139 total) demonstrated 4.8 point reduction in ESS; 84% of IH group continued therapy	Not available in the United States for any indication; EMA orphan designation	Echocardiogram recently required but no valvulopathy or pulmonary hypertension in the 45 patients studied; QT prolongation, dry mouth, palpitations, ventricular hyperexcitability, anorexia, nervousness, headaches
• Levothyroxine (73)	25 mcg/day	Clinical series of 9 previously-untreated IH patients (with normal thyroid function) demonstrated reduction in sleep time from 12.9 hours to 8.5 hours and reduction of 5.5 points on ESS at 8 weeks	Widespread	None seen in (73); known serious effects include arrhythmias, heart failure, hypertension, angina, and seizures
• Transcranial direct current stimulation (74)	3 stimulations per week x 4 weeks, performed between 8 and 11 am to avoid disturbing nocturnal sleep	Pilot study of 8 previously untreated IH patients showed 5.75 point decrease in ESS, 7/8 reporting improvement in sleepiness, and improvements in reaction times on attention test	Limited	Not reported in (74). Headache, sensory discomfort, and skin burns may occur (75).

* None of these treatments are approved by the US FDA for the treatment of idiopathic hypersomnia. Some of these medications (i.e., pitolisant, mazindol) are not approved by the US FDA for any indication.