Neurotherapeutics (2021) 18:20–31
https://doi.org/10.1007/s13311-020-00919-1

REVIEW

Idiopathic Hypersomnia and Other Hypersomnia Syndromes

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Published online: 8 September 2020

Abstract

There are numerous disorders of known or presumed neurologic origin that result in excessive daytime sleepiness, collectively known as the central disorders of hypersomnolence. These include narcolepsy types 1 and 2, idiopathic hypersomnia, Kleine–Levin syndrome, and hypersomnia due to or associated with medical disease, neurologic disease, psychiatric disease, medications or substances, and insufficient sleep durations. This chapter focuses on the treatment of nonnarcoleptic hypersomnia syndromes, from those that are commonly encountered in neurologic practice, such as hypersomnia due to Parkinson's disease, to those that are exceedingly rare but present with dramatic manifestations, such as Kleine–Levin syndrome. The level of evidence for the treatment of sleepiness in these disorders is generally lower than in the well-characterized syndrome of narcolepsy, but available clinical and randomized, controlled trial data can provide guidance for the management of each of these disorders. Treatments vary by diagnosis but may include modafinil/armodafinil, traditional psychostimulants, solriamfetol, pitolisant, clarithromycin, flumazenil, sodium oxybate, melatonin, methylprednisolone, and lithium.

Keywords Idiopathic hypersomnia · Kleine–Levin syndrome · modafinil · psychostimulants · lithium · methylprednisolone

Introduction

The central disorders of hypersomnolence are a group of disorders manifesting primarily as excessive daytime sleepiness, either persistent or episodic. These include narcolepsy types 1 and 2, idiopathic hypersomnia, Kleine–Levin syndrome, hypersomnia due to a medical or neurologic disorder, hypersomnia due to medication or substance, hypersomnia associated with psychiatric disorders, and insufficient sleep syndrome. Numerous controlled trials have evaluated treatment strategies for narcolepsy, particularly narcolepsy type 1 but also narcolepsy type 2. In contrast, very few controlled trials are available to guide treatment decisions for the other central disorders of hypersomnolence, and reliance on published clinical series, understanding of drug mechanisms, and off-label use of medications approved for narcolepsy is often necessary for their management. This chapter focuses on the management of this latter group of hypersomnia disorders.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is a central disorder of hypersomnolence that results in daily excessive daytime sleepiness, in the absence of another identified cause. Although sleepiness may sometimes be the only manifestation, it is often accompanied by long sleep durations at night, long naps, a sense of unrefreshing sleep, and great difficulty in awakening, known as sleep drunkenness or pronounced sleep inertia [1]. Fatigue, cognitive symptoms, and autonomic symptoms are common and contribute to the burden of disease [2–4].

Diagnostic criteria require the presence of daily excessive sleepiness for at least 3 months and objective measurement of increased sleep propensity [5]. The latter can be accomplished either via a multiple sleep latency test showing a mean sleep latency of less than or equal to 8 min or via extended monitoring of sleep durations showing sleep of at least 11 h per 24-h period. This can be done with in-laboratory polysomnography, for which multiple protocols have been developed [6–8]. Long sleep durations can also be

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demonstrated using ambulatory actigraphy, worn for at least 1 week of ad-lib sleep, although this has not yet been well-validated for this purpose [5]. The diagnosis of IH also requires ruling out other causes of sleepiness, including insufficient sleep durations, narcolepsy, and any other diagnosis that better explains the symptoms.

The population prevalence of IH has not been well-defined. IH is sometimes described as rare. In contrast, sleep durations of at least 9 h in association with distress or impairment are not rare, present in 1.6% of the population [9]. Because there are many causes of sleepiness and long sleep duration, no definitive biomarkers for IH, and no clear consensus about exactly which disorders must be ruled out before diagnosing IH, true prevalence of IH is difficult to establish. Some clinical series suggest a female preponderance, and onset is most commonly in late adolescence or early adulthood.

At present, there are several theories regarding the cause or causes of IH, but these await further investigation and the underlying pathophysiology of this disease is unknown. Hypocretin and histamine (the neurotransmitters of 2 main arousal systems) are not deficient in the cerebrospinal fluid (CSF) of IH patients. Candidate theories include increased activity of the sedating GABA-A system [10], circadian dysfunction resulting in long period length or decreased amplitude of circadian signals [11], changes in regional brain activity or connectivity [12, 13], or autonomic nervous system dysfunction [4, 14].

Treatment of IH focuses on management of its symptoms, especially but not only excessive daytime sleepiness. No disease-modifying or curative treatments are available. As of this writing, there are no medications that are approved by the US Food and Drug Administration (FDA) for the treatment of IH. Therefore, all treatments prescribed for people with IH represent "off-label" prescribing. Because the core symptom of IH is excessive daytime sleepiness, treatments known to help in other disorders of excessive daytime sleepiness, especially narcolepsy, are typically used. Further, it is currently unclear whether IH and narcolepsy type 2 represent distinct or overlapping disorders [15], so medications known to be beneficial in people with narcolepsy type 2 may be especially pertinent.

Modafinil and Armodafinil

Modafinil (and its r-enantiomer, armodafinil) is considered by some to be first-line for the treatment of IH in adults. Modafinil is a racemic mix of 2 enantiomers, r- and s-modafinil. Its full mechanism of action for wake promotion is not known, although a major mechanism of action is the prevention of dopamine reuptake [16]. It is approved by the US FDA for the treatment of sleepiness associated with either type of narcolepsy, obstructive sleep apnea, and shift work sleep disorder, in adults.

A single randomized, controlled trial (RCT) limited to adults with IH has been published comparing modafinil to placebo [17]. Thirty-one participants with IH without long sleep time, i.e., habitual nocturnal sleep duration of < 10 h, were included. Participants received modafinil 100 mg in the morning and 100 mg at noon, or matched placebo, for 3 weeks in this parallel-group study. Modafinil significantly improved sleepiness as measured by the Epworth Sleepiness Scale, with a significant reduction of 4.5 points more in the modafinil group than in the placebo group. Modafinil also resulted in a significant improvement in Clinical Global Impression scores of 1 point more than placebo. However, maintenance of wakefulness test scores were not reduced significantly more with modafinil than with placebo [17]. Of note, the dose used in this study was chosen to minimize adverse events and is below the FDA listed maximum dose of 400 mg/day.

Two additional modafinil RCTs have included patients with IH as well as those with narcolepsy, although these 2 reports from the same investigative group do not provide treatment data specific to those with IH [18, 19]. Participants in these 2 cross-over trials received modafinil 200 mg in the morning and 200 mg at lunchtime, or matched placebo, for 5 days. Considering all the hypersomnolent patient groups together, modafinil significantly improved sleepiness as measured by the maintenance of wakefulness test and improved driving performance [18, 19]. Because no analyses specifically assessed the effects of modafinil in the IH group alone, these studies do not directly indicate a treatment benefit of modafinil for people with IH. However, the majority of patients in these 2 studies (31/54, 57%) had IH, making it unlikely that these significant treatment benefits would be seen without a benefit in the IH group.

A fourth modafinil RCT, limited only to people with IH, the majority without long sleep times, has been completed and published in abstract form. This study also suggested a beneficial effect of modafinil in people with IH, but awaits full publication of results [20].

In addition to these RCTs, clinical experience also supports the usefulness of modafinil for adults with IH, at least in some patients. Four observational studies of modafinil, 3 retrospective and 1 prospective, have included a total of 230 people with IH [21–24]. Total daily doses of modafinil ranged from 100 to 1600 mg, the latter far exceeding the current FDA recommended maximum of 400 mg and a clear outlier. These clinical series suggest a benefit of modafinil on Epworth sleepiness scores (3-6 points of improvement measured prepost treatment) [22, 24]. One of these studies reported clinical improvement with modafinil in 83% of IH patients [21], while the other showed a complete response rate of 36%, a partial response rate of 8%, and a poor response rate of 56% [23].

Armodafinil is the r-enantiomer of modafinil. It has the same FDA indications as modafinil and is also not labeled

for use in treatment of IH. Armodafinil has not been studied in RCTs of IH, nor are there published case series in this population. However, based on its pharmacology, it is presumed to have similar effectiveness to modafinil in people with IH. Unlike modafinil, which is frequently prescribed in divided doses to ensure wake-promoting effects last throughout the afternoon and early evening [25], armodafinil is usually taken as a single morning dose, which may be more convenient for patients.

Based on clinical trials for other indications, commonly observed side effects of modafinil and armodafinil include headache, anxiety, and palpitations [26]. Insomnia may be seen, especially with armodafinil or dosing either medication too close to bedtime. Serious side effects of modafinil and armodafinil include Stevens–Johnson syndrome, angioedema, psychosis, mania, hallucinations, suicidal ideation, and dependency or abuse. Serious drug rashes requiring drug discontinuation may occur in adults or children, but appear more common among children, for whom use of modafinil and armodafinil is not FDA-approved for any indication [26]. Although severe drug rash syndromes are very rare, milder rashes may occur with use of modafinil and armodafinil. Because serious and nonserious rashes cannot be reliably distinguished at onset, people treated with these medications should be instructed to discontinue the medication at the onset of any rash. Because of some abuse potential, modafinil and armodafinil are FDA schedule IV medications.

Modafinil and armodafinil are strong inducers of the CYP3A4 system and weak inhibitors of the CYP2C19 system, which increases their potential for drug–drug interactions. Although numerous potential interactions exist, one of particular relevance is that between modafinil/armodafinil and hormonal birth control, reducing the effectiveness of contraception. As a result, women of childbearing potential treated with modafinil or armodafinil should be advised to use an additional or alternate birth control method during treatment with modafinil/armodafinil and for 28 days after their discontinuation [26]. Current FDA labeling for modafinil and armodafinil advises that patients consider avoiding use during pregnancy, based on a lack of data sufficient to assess risk but evidence of embryo–fetal toxicity in animal studies. In several other countries, recommendations to avoid use of modafinil during pregnancy have recently been issued, based on concerns for fetal risk from an ongoing registry [27]. A Danish study identified 49 pregnancies exposed to modafinil and compared them to nonexposed pregnancies and 963 pregnancies exposed to methylphenidate [28]. There were 6 major malformations in the modafinil-exposed pregnancies, yielding a crude odds ratio for major congenital malformations of 3.4 with modafinil compared to nonexposed pregnancies (adjusted odds ratio of 2.7, controlling for comorbidities and other exposures) and of 3.0 for modafinil compared to methylphenidate (adjusted odds ratio 3.4).

Sympathetomimetic Psychostimulants

Traditional psychostimulants are sometimes used in the treatment of IH, especially when modafinil/armodafinil are ineffective, not tolerated, or contraindicated. Numerous sympathomimetic psychostimulants are FDA-approved for the treatment of narcolepsy, attention deficit hyperactivity disorder (ADHD), or both, but none is FDA-approved for the treatment of IH. In the USA, available psychostimulants include methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, lisdexamfetamine, methamphetamine, and combinations of some of these. Many of these medications are available in both immediate- and extended-release preparations.

No RCTs of these medications have been performed for the treatment of IH and, although these medications are FDA-approved for the treatment of narcolepsy, relatively few RCTs have been performed testing this class of medications for the treatment of narcolepsy [29]. Although clinical trial data are limited, this class of medications is recommended for the treatment of narcolepsy with a moderately strong recommendation [29], and this class of medications has long been used for the treatment of disorders of excessive daytime sleepiness.

Methylphenidate response in IH patients has been evaluated in a single retrospective case series including 61 patients [23]. In this series, the mean dose was 51 mg. Sixty-six percent of patients remained on treatment with methylphenidate throughout the monitoring period. Of these, 25 (41% of the total IH group) were considered complete responders, similar to the response rate with modafinil. Published data using other psychostimulants in IH are even more sparse. A series of 8 IH patients treated with amphetamine–dextroamphetamine identified 50% who remained on treatment throughout the monitoring period, with 25% of the whole group (i.e., 2 patients) having complete response to treatment [23]. Two small series of IH patients, comprising a total of 15 patients, identified only 5 responders to dextroamphetamine (33%) [22, 23].

Common side effects of traditional psychostimulants include irritability, tachycardia/palpitations, anxiety, insomnia (especially if dosed too close to bedtime), and increases in blood pressure [30]. Rare but serious side effects of traditional psychostimulants include dependence and abuse, psychosis, behavior changes, mood changes, arrhythmias, hypertension, other cardiac disease, seizures, hepatotoxicity, pancytopenia, and erythema multiforme. Because of the risk of abuse, these medications are FDA schedule 2 and have black box warnings for abuse and dependence. Some traditional psychostimulants are FDA-approved for use in children, for indications other than IH, particularly attention deficit hyperactivity disorder and narcolepsy. The FDA recommends against use of most traditional psychostimulants during pregnancy, although states that methylphenidate may be used with caution, with some evidence of harm in animal data at supramaximal doses.

Solriamfetol

In March 2019, the FDA approved a novel wake-promoting medication, solriamfetol, for the treatment of sleepiness associated with narcolepsy or obstructive sleep apnea. It is a dopamine and norepinephrine reuptake inhibitor. To date, this medication has not been studied for the treatment of sleepiness associated with IH, but consideration of off-label prescribing for people with IH may be reasonable given its effects on reducing sleepiness caused by multiple different pathophysiologic mechanisms (i.e., hypocretin deficiency, sleep apnea, and narcolepsy type 2). However, solriamfetol is not approved for use in children for any indication. Common side effects are similar to those seen with other wake-promoting medications and include headache, anxiety, palpitations, and insomnia [31]. Small average increases in heart rate and blood pressure were seen in clinical trials for other indications [32, 33]. There is a risk of abuse and dependence, and this medication is FDA schedule 4.

Pitolisant

Pitolisant, a histamine H3 inverse agonist/antagonist, has been approved for the treatment of narcolepsy by the European EMA for several years and was recently approved for the treatment of narcolepsy by the FDA. Pitolisant has not been tested in a placebo-controlled trial of people with IH. In a small case series of IH patients whose symptoms could not be adequately controlled with modafinil, methylphenidate, or sodium oxybate, pitolisant was effective in reducing sleepiness (defined as a reduction in Epworth scores of at least 3 points compared to baseline) in 37% of people with IH with long sleep times and 31% of people with IH without long sleep times [34].

Pitolisant is not approved for use in children for any indication. Common side effects include headache, insomnia, nausea, and anxiety. Pitolisant prolongs the QT interval, so EKG should be performed, especially in those with liver or kidney disease, which can slow the clearance of pitolisant. Current FDA labeling advises that there is a potential for interaction with hormonal birth control, such that additional or alternate methods of contraception should be used while taking pitolisant and for 28 days after discontinuation of pitolisant. However, recent data published in abstract form suggest that pitolisant's action as a CYP 3A4 inducer is only weak [35]. Caution is advised during pregnancy due to presence of birth defects in animals [36]. Pitolisant is a prescription medication but is not a controlled substance; it is unscheduled by the FDA.

Clarithromycin and Flumazenil

Based on the hypothesis that IH may be caused by an endogenous substance that increases activity at sedating GABA-A receptors [10], treatment of IH with antagonists or negative modulators of GABA-A receptors is sometimes considered. Currently available medications for this are clarithromycin and flumazenil; other similar compounds are undergoing clinical trial evaluation.

Clarithromycin, a macrolide antibiotic, modulates the function of GABA-A receptors [37, 38]. In a pilot, cross-over RCT of 20 patients with IH and other similar hypersomnolence disorders, clarithromycin reduced subjective sleepiness as measured by the Epworth and improved measures of quality of life, although did not improve performance on the psychomotor vigilance task (PVT), the primary and objective outcome measure [39]. In a published clinical series of clarithromycin use in people with hypersomnia disorder including IH, refractory to other wake-promoting medications, 64% of patients reported symptomatic benefit and 38% continued treatment on a chronic basis after weighing the magnitude of this benefit against the experienced and potential risks. Common side effects of clarithromycin include gastrointestinal upset and taste perversion. Serious side effects of clarithromycin include antibiotic resistance, superinfection with infections such as *Clostridium difficile*, QT prolongation, and increased mortality in people with a history of myocardial infarction or angina [40, 41]. Drug–drug interactions are based on its actions as an inhibitor of CYP2C9, 3A4, P-gp, and OATP1B1. Clarithromycin requires prescription but is not a controlled substance.

Flumazenil is a negative allosteric modulator of GABA-A receptors, in addition to its role as a competitive antagonist at the benzodiazepine binding site [10]. When given intravenously in a single-blind fashion to hypersomnolent patients, it significantly improved sleepiness, as measured by the Stanford Sleepiness Scale, and improved reaction times on the PVT [10]. However, its duration of action on sleepiness symptoms is short, requiring multiple doses per day, requiring compounding into a nonintravenous form. Because of a very large first-pass metabolism effect, oral preparations are impractical, and it has instead been compounded as transdermal, sublingual, or subcutaneous for the treatment of IH [42, 43]. In a series of 153 patients with IH and related hypersomnolence disorders, refractory to standard treatments, flumazenil reduced symptoms of sleepiness in 62.8%, and 38.6% chose to remain on this medication chronically [42]. Serious side effects for intravenous flumazenil are well characterized and include seizures and arrhythmias. Side effects of compounded flumazenil are not as well understood, given the relatively limited use of flumazenil in this manner, and the potential for serious side effects must be taken into consideration before flumazenil is prescribed.

Sodium Oxybate

All of the previously discussed treatments for IH are dosed during the day to promote wakefulness directly. Sodium oxybate is a GABA-B agonist that instead is dosed at bedtime and during the night, resulting in improved nocturnal sleep quality and reduction of daytime sleepiness and cataplexy in people with narcolepsy [29]. It is FDA-approved for the treatment of narcolepsy in adults and children. Because nocturnal sleep quality is better in IH than in narcolepsy type 1 [44], it is not as clear whether sodium oxybate would be useful for people with IH. Additionally, sleep inertia is worsened in healthy people with increasing amounts of N3 sleep [45], raising concern that sodium oxybate might worsen sleep drunkenness via medication-induced increases in N3 sleep.

However, the small amount of published clinical experience with sodium oxybate in IH does not support these concerns, instead suggesting similar effectiveness in those with IH and those with narcolepsy with cataplexy [46]. In this patient series of approximately 40 people with IH, the reduction in Epworth scores was similar between people with IH and those with NT1, and 71% of IH patients treated with sodium oxybate also demonstrated an improvement in sleep drunkenness.

Common adverse events from sodium oxybate include nausea, bed-wetting, and dizziness. Based on the single case series, side effects from sodium oxybate may be more common in those with IH, particularly nausea and dizziness [46]. Serious side effects of sodium oxybate include central nervous system and respiratory depression, psychosis, depression, suicidal ideation, and abuse or dependence. Because the related compound gamma-hydroxybutyrate (GBH) is an illicit drug of abuse, there is a potential for sodium oxybate diversion. In cases of misuse, sodium oxybate may result in seizures, coma, or death. Sodium oxybate must be dispensed under an FDA REMS (Risk Evaluation and Mitigation Strategy) program and is dispensed directly through a centralized pharmacy. Caution is advised during pregnancy, based on inadequate human data to assess risk.

Management of IH Symptoms Beyond Excessive Daytime Sleepiness

In addition to treatment of sleepiness, it is often necessary to treat sleep inertia in people with IH, although there are no medications specifically approved or tested for this symptom. Clinical experience has suggested that use of wake-promoting medications at bedtime, including traditional stimulants, can help with sleep inertia on morning awakening [1], although these medications may not be tolerated at bedtime due to insomnia. Delayed-release methylphenidate, taken at bedtime for the treatment of next-day ADHD symptoms, might be particularly beneficial for the treatment of sleep inertia, because it ensures morning bioavailability of methylphenidate without as much risk of insomnia as with bedtime dosing. However, this strategy awaits formal testing.

For patients who cannot tolerate immediate- or extended-release wake-promoting medications at bedtime, a common strategy to manage sleep inertia involves setting 2 alarms, approximately 1 h apart, the first 1 h before desired awakening and the second at the time of desired awakening. When the first alarm awakens the patient, the morning dose of wake-promoting medication is taken, then the patient returns to sleep until the second alarm. By the time of the second alarm, absorption of wake-promoting medication over the prior hour will theoretically help counter sleep inertia. However, this strategy also awaits controlled evaluation. It also may require the assistance of a family member or caregiver, in severe cases where sleep inertia prevents waking enough to take medications. It has been speculated that bedtime melatonin might be beneficial for reducing sleep inertia, because sleep inertia may be exacerbated by the delayed sleep phase seen in many people with IH and melatonin can cause phase advance [6].

Long sleep durations are another problematic symptom for many people with IH. Because long sleep durations are atypical in narcolepsy, especially in narcolepsy with cataplexy [47], clinical trials of narcolepsy treatments often have not assessed changes in sleep duration as a treatment outcome. It is therefore difficult to predict their efficacy (or lack thereof) in shortening sleep duration in those with IH. The only modafinil RCT limited to those participants with IH did not enroll IH participants with long sleep times [17], so does not inform the question. Considering all participants, including only half with IH and only a quarter with IH with long sleep time, there was no significant reduction in nocturnal sleep time in the clarithromycin RCT [39].

"Brain fog" or cognitive dysfunction is a common symptom of IH, although it is presently unclear whether this reflects a nonspecific vigilance decrement due to sleepiness itself [48] or might be a disease-specific manifestation of IH that reflects difficulty with sustained attention for long time periods [49]. To the extent that cognitive symptoms are a manifestation of sleepiness, they would be expected to improve alongside improvement in sleepiness with medication, whereas if they are distinct from sleepiness, they may need separate, targeted interventions. At present, there are no data to guide treatment of this common and problematic symptom of IH. School or work accommodations may be beneficial, although may be different than those typically recommended for people with narcolepsy. In particular, short scheduled naps may help some people manage narcolepsy symptoms, but are less useful for people with IH who require long naps and waken unrefreshed. Individual accommodations may include additional time on testing and assignments, delayed morning start time, excused absences related to medication holidays or prolonged sleep durations, and multiple others based on the individual's needs.

Hypersomnia Due to a Medical or Neurologic Disease

Excessive sleep time and excessive daytime sleepiness can be comorbid to several neurodegenerative (e.g., Parkinson's disease or dementia with Lewy bodies [50]), genetic (e.g., Prader–Willi syndrome [51], muscular dystrophies), tumoral (e.g., craniopharyngioma), vascular, or inflammatory insults to the central nervous system. More commonly, around 10% of patients with severe obstructive sleep apnea syndrome may suffer from residual sleepiness despite adequate positive airway pressure [52]. This may rarely but possibly be associated with abnormal multiple sleep latency test or long sleep time on formal sleep tests [53], suggesting long-term damage to arousal systems. Traumatic brain injury may lead to posttraumatic hypersomnia or "pleiosomnia" (this term means that the mean daily amount of sleep and the multiple sleep latency test are abnormal in patients after traumatic brain injury, compared to healthy controls [54], without always reaching the values observed in IH), possibly linked with damage in arousal networks [55]. Postviral hypersomnia may occur shortly after infections with Epstein–Barr virus.

Very limited RCT data are available to guide management of hypersomnias due to medical or neurologic disorders, although those medications effective for narcolepsy may be considered for off-label use. The exception is obstructive sleep apnea, for which there are 3 medications that are evidence-based with high-grade evidence and FDA-approved for sleepiness in sleep apnea: modafinil [56], armodafinil [57], and solriamfetol [32]. In addition to the classical side effects of the 3 drugs, consideration should be given to their potential increased risk in OSA patients with concomitant hypertension.

Although hypersomnia due to medical conditions are considered a single entity for diagnostic purposes, it is likely that different medical and neurologic causes of hypersomnia may require different treatments. For hypersomnia due to Parkinson's disease, modafinil has been shown to be beneficial in meta-analysis of several small RCTs, with a mean reduction of 2.3 points in the Epworth compared to placebo [58, 59]. In a single crossover RCT of 12 participants, sodium oxybate also reduced sleepiness in people with Parkinson's disease [60], although careful attention should be paid to risks of sodium oxybate that may be magnified in people with Parkinson's disease. In hypersomnia due to traumatic brain injury, 2 RCTs have yielded conflicting results, with a treatment benefit measured by Epworth in 1 but not the other [61, 62]. An RCT of armodafinil enrolling 117 participants with traumatic brain injury found no benefit on self-reported sleepiness as measured by Epworth, although multiple sleep latency test did significantly lengthen [63]. Modafinil may have a modest treatment benefit on sleepiness due to myotonic dystrophy, reducing Epworth scores by 1.6 points more than placebo in meta-analysis of scant available studies [64].

Hypersomnia Comorbid to Psychiatric Disease

Hypersomnolence, broadly defined as excessive daytime sleepiness and/or excessive sleep duration, commonly occurs in patients with psychiatric disorders, but is rarely studied [65]. Although mood disorders are classically associated with insomnia rather than hypersomnia, atypical depression is characterized by a complaint of prolonged sleep time and sleep inertia, congruent with depressive mood (with a classical improvement of both mood and alertness later in the day). Fluctuating sleep times, which oscillate from reduced sleep time with absent daytime sleepiness (and frequent elation) for a few days followed by a progressive increase of sleep time (which may reach a maximum of 15 h in bed, in association with low mood and motivation), are classical in bipolar disorders, even without frank manic or depressive switches. In seasonal affective disorders, patients have increased sleep time, apathy, and decreased mood during winter. In all these cases, objective sleep tests may find either no increased sleep time or no shortened multiple sleep latency test despite long time in bed (a condition named clinophilia [66]) or, on the contrary, may find objective increase in nighttime sleep duration and abnormal multiple sleep latency test values (below 8 min, but rarely below 5 min) [65, 67]. The presence of hypersomnia in mood disorders may be a marker of severity, associated with more frequent suicidal attempts and resistance to treatment [65]. The mechanisms of hypersomnolence in association with major depressive disorder are yet unknown, but may include impairment in the thalamostriatal connectivity [68].

As in hypersomnia due to medical and neurologic disease, there are very limited clinical trial data to guide treatment decisions in caring for people with hypersomnia comorbid to mood disorders, and off-label prescription of medications to improve wakefulness may need to be considered. Modafinil is sometimes used as adjunctive therapy for depression with hypersomnia symptoms; however, 2 RCTs of modafinil in hypersomnia associated with major depression have not provided clear or sustained evidence of benefit on sleepiness [69, 70]. As with hypersomnia due to medical or neurologic diseases, when treating patients for hypersomnia comorbid to psychiatric disorders, it is important to consider whether the comorbid illness will increase risk for side effects with any particular wake-promoting medication.

Hypersomnia Due to a Medication or Substance and Insufficient Sleep Syndrome

In hypersomnia due to a medication or substance, sleepiness is attributable to use of a medication with sedating properties or withdrawal of medication with alerting properties. In either case, management involves minimizing or discontinuing the offending agent. Insufficient sleep syndrome is defined as sleepiness caused by failure to obtain sleep amounts expected for age [5]. As such, primary treatment involves sleep extension, which may require targeted interventions to address the barriers to obtaining enough sleep, such as work and family responsibilities.

Kleine–Levin Syndrome

Kleine–Levin syndrome (KLS) is a rare disorder marked by relapsing–remitting episodes of hypersomnia, mainly affecting teenagers and with a male predominance [71–76]. KLS prevalence is estimated around 1 to 4 cases per million, 5% of which are familial [75]. The consensus criteria for KLS diagnosis include at least 2 distinct episodes of 2 to 42 days, often recurring at least once per year, with normal sleep, mood, behavior and cognition between episodes, and no better explanation for the symptoms [5]. The episodes should contain a severe hypersomnia, combined with at least 1 of the following: cognitive dysfunction, altered perception, eating disorders (either excessive or reduced intake), or disinhibited behavior. Hypersomnia is a mandatory symptom, at least during the first years of the disease. The duration of sleep is prolonged (especially in teenagers) with a median 18-h sleep per day. Most patients are difficult to awaken, but remain arousable, waking up spontaneously to void and eat. Other core symptoms are almost always present, at least during the first years of the disease, including cognitive impairment, derealization, apathy, and psychological changes. Derealization affects more than 9 in 10 patients and is strongly linked to hypoactivity of the right temporoparietal junction on functional imaging [77]. A striking apathy affects nearly all patients [71]. The frequency of other symptoms such as hypersexuality, hyperphagia, hallucinations, delusions, and headache is lower and varies among patients and between episodes.

Flattened affect and sad mood affect around half of the patients during episodes [73]. In rare cases, the sad mood overshoots the sleep episode. Most commonly, the termination of an episode is characterized by a deep feeling of relief, logorrhea, elation, and insomnia, for 1 or 2 days, as if patients were trying to make up for the lost time. Anxiety is reported by 70% of the patients during an episode. Anterograde amnesia is frequent, with patients having no or only partial recall of the episode. Photophobia and painful hyperacusis are frequent. Other autonomic signs are exceptional. They include abnormally high or low blood pressure, bradycardia or tachycardia, and ataxic respiration [78]. The pattern of blood pressure over 24 h is flattened, including a loss of the usual dip during the night and increase during the day [76].

Episodes last a median 13 days, occurring every 3 to 6 months on average [79]. However, the picture varies from short episodes (e.g., 7 days) occurring every month in young patients to prolonged episodes longer than 1 month (in 1/3 of the patients) with mostly apathy and altered cognition [73, 75]. The frequency and duration of episodes are unpredictable, although patients with long episodes at KLS onset usually continue to have long episodes and longer disease duration [75]. Over the course of several years, the frequency (but not the duration) of episodes often lessens, with episodes containing less sleep, which unmasks the other symptoms including apathy, derealization, and major fatigue [71].

There is an identifiable trigger just before the first episode in 89% of the cases, including infections (72%), alcohol intake (23%), sleep deprivation, unusual stress, and head trauma [71]. The same triggers can be found, although less frequently, for subsequent episodes [74]. Some episodes may also appear around menstruation, but this is usually irregular, suggesting the link is weak. The median disease course is around 15 years [71]. Rare patients have late relapses, sometimes after 10 to 15 years without episodes [71, 75].

Routine electroencephalography (EEG) obtained during episodes shows general or focal slowing of background in 70% of cases and often demonstrates paroxysmal 0.5- to 2-s bursts of bisynchronous, generalized, moderate- to high-voltage 5- to 7-Hz waves [71]. Sleep studies during episodes are often difficult to interpret, because results are dependent on whether sleep was monitored only for the night or during the whole 24 h, at the beginning *versus* the end of episodes, or at onset of the disease or later in its course. Twenty-four–hour polysomnography demonstrates prolonged total sleep time (12-14 h) [72, 80], up to 18 h or more in some reports. Sleep efficiency is decreased, with frequent awakenings, excess of stages N1 and N2 [80], decreased N3 sleep during the first half, and decreased rapid eye movement (REM) sleep during the second half of episodes [81]. Results of the multiple sleep latency tests are dependent on the subject's willingness to comply with the procedure, and may either be normal or abnormal, showing short latencies or multiple sleep onset REM periods, with up to 21% patients having a narcolepsy-like pattern [79]. With disease progression, patients may not sleep continuously but instead may stay in their bed with eyes closed.

Computed tomography scans and magnetic resonance imaging are typically normal or contain incidental findings unrelated to the disease. In contrast, brain functional imaging is abnormal in most cases, with hypoperfusion of the left or right temporal–parietal junction, as well as the diencephalon. Some hypermetabolism, possibly compensatory, can be seen in

some frontal areas. These abnormalities are present both during and between the episodes of hypersomnolence. CSF white cell and protein counts are normal, ruling out meningitis. There was no oligoclonal CSF secretion of antibodies (as in multiple sclerosis, another remittent neurological disease), in 4 KLS patients. The CSF levels of hypocretin-1 are lower (but not absent, as in narcolepsy type 1) or within normal ranges during episodes with a normalization during asymptomatic periods [76, 82], seemingly not low enough to explain the level of hypersomnia observed during episodes.

During asymptomatic periods, KLS patients have, on average, similar scores on sleep, apathy, derealization, eating behavior, anxiety, and mood scales than controls [73, 75]. However, when 124 patients with KLS had systematic cognitive assessment during asymptomatic periods, they showed lower logical reasoning and nonverbal intelligence quotient, slower speed of processing, reduced attention, and reduced retrieval strategies in episodic verbal memory compared to controls [83]. Specifically, 37% of KLS patients had altered immediate episodic verbal memory (but not delayed recall), indicating a difficulty in the retrieval of information immediately after encoding. Executive functions, visuo-constructional abilities, and nonverbal memory were intact. In a cohort of 115 young KLS patients, regular psychiatric evaluations indicated some comorbid psychiatric disorders during "asymptomatic periods" in 21% of patients after KLS onset [84]. Among them, mood disorders were prominent, followed by anxiety disorders and miscellaneous psychiatric disorders. Because anxiety and mood disorders are the most common psychiatric disorders associated with chronic medical illnesses, this outcome is not surprising. The risk factors for emerging psychiatric disorders included female sex, longer KLS course, longer time incapacitated, and more frequent psychiatric symptoms during episodes. This result suggests a need to regularly assess mental health in patients with KLS during follow-up.

As the disease is exceptionally rare, several more common diagnoses are usually considered first (Table 1). When brought to the emergency room during an episode, most patients undergo a classical workup for acute confusion and sudden behavioral changes in teenagers: checking for alcohol, drug, and illegal substance intake; MRI to rule out tumor, traumatic, or inflammatory diseases of the brain, multiple sclerosis, and stroke; an EEG to exclude status epilepticus; and a lumbar puncture (especially in a context of fever) to exclude encephalitis (mostly herpetic encephalitis and NMDA encephalitis). Tumors within the third ventricle may produce intermittent obstructions of ventricular flow, leading to headaches, vomiting, vague sensorial disturbances, and a paroxysmal impairment of alertness. Severe basilar migraine and temporal lobe epilepsy less frequently mimic some symptoms of KLS. Recurrent episodes of sleepiness are also reported in the context of psychiatric disorders, such as depression, bipolar disorder, seasonal affective disorder, and somatoform disorder. Hallucinations and delusions in a previously normal teenager are evocative of brief psychosis episodes. Excessive sleepiness in other sleep disorders occurs daily and is usually not recurrent, except that the level of sleepiness may fluctuate in some patients with IH. "Idiopathic" stupor is a rare and debated entity, occurring usually in middle-age subjects, with stupor episodes lasting no more than 48 h, associated with benzodiazepine intoxication.

The cause of KLS is still unknown. Most KLS symptoms (derealization, apathy, deinhibition) are suggestive of transient alterations of the associative cortices. There is no clear cause of the striking hypersomnia, as KLS patients are not hypocretin- or histamine-deficient. The dysfunction of the thalamus may reduce alertness, as in hypersomnia associated with bithalamic ischemia [85]. Functional brain imaging studies during episodes are frequently abnormal, showing hypometabolism in the thalamus, hypothalamus, mesial temporal lobe, and frontal lobe. Some of these abnormalities persist during asymptomatic periods in half of the patients [77, 85]. A controlled whole brain voxel-based group analysis using SPECT found that 41 patients during asymptomatic periods had persistent hypoperfusion in the hypothalamus, the thalamus (mainly the right posterior part), the caudate nucleus, and cortical associative areas, including the anterior cingulate, the orbito-frontal, and the right superior temporal cortices, extending to the insula [77]. Two additional

Table 1 Differential diagnosis in KLS

Neurological disorders	Psychiatric disorders	Sleep and medical disorders
Complex partial seizures	Alcohol, drugs, and illegal substances intake	Post-viral hypersomnia
Severe basilar migraine	Depression	Narcolepsy
Encephalitis	Bipolar disorder (rapid cyclic)	IH (with fluctuating sleep times)
Trauma, stroke, or inflammation	Seasonal affective disorder	Idiopathic recurrent stupor
Tumors within the 3rd ventricle	Somatoform disorder	Ornityl-carnitine transferase deficit
	Brief psychotic episode	Intermittent porphyria

hypoperfused areas emerged during symptomatic periods, located in the right dorsomedial prefrontal cortex and the right parieto-temporal junction. The derealization during symptomatic periods strongly correlated with the hypoperfusion of the right and left parieto-temporal junctions.

An epileptic cause for KLS has been ruled out by examination of the EEG (no epileptic findings) and by lack of efficacy of antiepileptic medication during episodes. There is some evidence for a recurrent, localized inflammatory encephalitis, including mild localized encephalitis in 3 cases with postmortem brain examination. An autoimmune or inflammatory origin for KLS is additionally suggested by onset during adolescence, frequent infection at onset, relapsing–remitting aspect, and benefit of lithium (which has anti-inflammatory properties) and intravenous steroids [86–89]. However, no HLA association was reproduced in large series [73, 75], and serum cytokine levels were normal [90]. As for genetic hypotheses, although familial risk is low (1% per first-degree relative), 5% of cases have an affected family member [73]. There are, to date, 19 multiplex families containing 2 to 6 affected members and 4 pairs of monozygotic twins [91, 92]. Karyotyping was normal in 112 patients [92]. Exome sequencing in familial cases did not yield any specific gene [93]. Genome-wide association in more than 400 patients suggests that a polymorphism in Trank1 gene is more frequent in affected patients (mostly those with birth defect) than in controls (Mignot, personal communication).

General Management of KLS

Many patients benefit from reassurance, simple hygiene rules (i.e., avoidance of triggers), and home management [71]. During the episodes, it is recommended to let the patient sleep at home in a familiar environment under family supervision, rather than hospitalizing them. This attitude reduces the anxiety related to novelty and the risk of embarrassing public behaviors, and is safer for the patient. Driving should be firmly forbidden during episodes, as sleepiness, automatic behavior, and altered perception increase the risk of a road accident. The family should regularly check during an episode to ensure the patient has no suicidal thoughts. Between episodes, patients should keep a regular sleep/wake schedule (as sleep deprivation can trigger episode) and avoid alcohol and contact with others who may be infectious.

Because attention, episodic memory, and speed of processing are affected in KLS patients between episodes, school accommodations may be beneficial, including a reduced workload at school, frequent breaks during homework, and extra time to complete exams. Cognitive remediation and methylphenidate may be considered on an individual basis.

Medications During KLS Episodes

Because KLS is extremely rare and episodic, no RCTs of treatment to treat or prevent episodes have been performed, and treatment options are largely informed by case series. Once an episode has started, there is little evidence that medications can stop its development. One promising agent is intravenous methylprednisolone 1 g/day for 3 days. In a case series, 26 KLS patients were treated with methylprednisolone during episodes (between 1 and 6 episodes each) and were compared to 48 untreated KLS patients [94]. Forty percent of treated patients experienced a shortening of episode duration by at least 1 week compared to their baseline, while only 10% of untreated patients had a similar shortening of episodes over time. Sixty-five percent of treated patients experienced shorter episodes when the methylprednisolone was given during the first 10 days of the episode [94]. This treatment is not recommended for brief (7-10 days) episodes, but rather for patients who have previously suffered long (> 30 days) episodes. Notably, intravenous steroids seem to be are well tolerated in this population, with a few minor (e.g., insomnia) side effects and no megaphagia or manic switching noted.

Two reports of clarithromycin for the treatment of KLS spells have been published, collectively describing 5 patients [95, 96]. All 5 patients experienced symptomatic benefit, through apparent truncation of an episode, reduction of symptom severity, or lengthening of time between episodes. In some cases, this benefit was transient and in others more sustained, and side effects were sometimes treatment limiting. As such, further evaluation for a potential role of clarithromycin during KLS spells is needed.

During KLS episodes, psychostimulants may partially improve alertness, but they have no effect on apathy, derealization, and confusion [73, 79, 86], and may increase the irritability of the patients. When psychotic symptoms are prominent, neuroleptics like risperidone seem to be helpful [73, 79]. When major anxiety occurs, a benzodiazepine can be of some help.

Medications Preventing New KLS Episodes

When episodes are frequent, disabling, or prolonged, preventive medications can be explored, notably lithium [97]. In a large, prospective, open-label, controlled study, 71 KLS patients treated with lithium therapy had superior outcomes to 49 KLS patients who were not treated with medication. With serum lithium levels kept between 0.8 and 1.2 mmol/L (measured 12 h after the drug intake), episodes completely stopped in 35% of patients on lithium (*vs* only 3% of the nonlithium group). Episodes were less frequent or less severe in another 45% of lithium-treated patients, with immediate relapses within 2 days when lithium was discontinued [97]. The potential risks of lithium therapy are thyroid and kidney insufficiency,

hence the importance of adequate hydration and regularly monitoring serum lithium level, thyroid-stimulating hormone, and creatinine. Antiepileptic mood stabilizers (e.g., valproate) seem less effective than lithium. In women with menstrual-associated KLS, estrogen–progesterone may be tried [98].

Although the studies discussed in this review can provide some guidance for the treatment of the nonnarcoleptic central disorders of hypersomnolence, it is clear that additional randomized, controlled trials are urgently needed. Endpoints for such studies should include excessive daytime sleepiness but also other symptoms of hypersomnolence that contribute to disease burden and functional limitations. Better understanding of the mechanisms underlying this group of diverse disorders is also needed, to inform development therapeutic options.

Acknowledgments This work was supported by the National Institutes of Health (R01 NS111280, to LMT), the KLS Foundation (to IA), and KLS-France (to IA). This work is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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