Idiopathic Hypersomnia and Other Hypersomnia Syndromes

Lynn Marie Trotti, Isabelle Arnulf

Idiopathic hypersomnia and other hypersomnia syndromes

Lynn Marie Trotti* and Isabelle Arnulf †

*Department of Neurology, Emory University School of Medicine, and Emory Sleep Center, Emory Healthcare, Atlanta, Georgia, USA

†Service des Pathologies du Sommeil, Centre National de Reference des Hypersomnies Rares, Hôpitaux Universitaires Pitié-Salpêtrière, Sorbonne Université, Paris, France

Article Type: Invited Review

Corresponding Author:

Lynn Marie Trotti, MD, MSc

12 Executive Park Dr NE

Atlanta, GA 30329

Lbecke2@emory.edu

(404) 712-7240

(404) 712-8145

Running title: Hypersomnia syndromes and KLS

Summary

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 non-narcoleptic 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 and 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 three 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 minutes or via extended monitoring of sleep durations showing sleep of at least 11 hours per 24-hour period. This can be done with in-laboratory polysomnography, for which multiple protocols have been developed [6-8]. Long sleep durations can also be demonstrated using ambulatory actigraphy, worn for at least one 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 hours 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. 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 United States 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 two 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 United States Food and Drug Administration (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 hours, were included. Participants received modafinil 100 mg in the morning and 100 mg at noon, or matched placebo, for three 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 two reports from the same investigative group do not provide treatment data specific to those with IH [18, 19]. Participants in these two cross-over trials received modafinil 200 mg in the morning and 200 mg at lunchtime, or matched placebo, for five 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 two 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 a some patients. Four observational studies of modafinil, three retrospective and one prospective, have included a total of 230 people with IH [21-24]. Total daily doses of modafinil ranged from 100 mg 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 scores (3-6 points of improvement measured pre-post 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 non-serious 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 non-exposed 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 non-exposed 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 are FDA-approved for the treatment of IH. In the United States, 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. Similar to modafinil and armodafinil, pitolisant is an inducer of CYP3A4, resulting in potential drug-drug interactions. Women of childbearing potential should thus use an alternate or additional form of contraception to birth control pills while taking pitolisant and for 28 days after discontinuing pitolisant. Caution is advised during pregnancy [35]. 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 [36, 37]. In a pilot, crossover 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 [38]. 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 [39, 40]. 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 non-intravenous 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 [41, 42]. 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 [41]. 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 [43], 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 [44], 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 [45]. 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 [45]. 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-hydroxy-butyrate (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 two alarms, approximately one hour apart, the first one hour 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 [46], 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 [38].

"Brain fog" or cognitive dysfunction is a common symptom of IH, although it is presently unclear whether this reflects a non-specific vigilance decrement due to sleepiness itself [47] or might be a disease-specific manifestation of IH that reflects difficulty with sustained attention for long time periods [48]. 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 [49]), genetic (e.g., Prader-Willi syndrome [50], 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 [51]. This may rarely but possibly be associated with abnormal multiple sleep latency test or long sleep time on formal sleep tests [52], suggesting long term damage to arousal systems. Traumatic brain injury may lead to post-traumatic 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 [53], without always reaching the values observed in IH), possibly linked with damage in arousal networks [54]. Post-viral 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 three medications that are evidence-based with high grade evidence and FDA-approved for sleepiness in sleep apnea: modafinil, armodafinil, and solriamfetol.

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 [55, 56]. In a single cross-over RCT of 12 participants, sodium oxybate also reduced sleepiness in people with Parkinson's disease [57], 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, two RCTs have yielded conflicting results, with a treatment benefit measured by Epworth in one but not the other [58, 59]. 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 latency did significantly lengthen [60]. 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 [61].

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 [62]. 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 [63]), 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) [62, 64]. The presence of hypersomnia in mood disorders may be a marker of severity, associated with more frequent suicidal attempts and resistance to treatment [62]. The mechanisms of hypersomnolence in association with major depressive disorder is yet unknown, but may include impairment in the thalamostriatal connectivity [65].

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 two RCTs of modafinil in hypersomnia associated with major depression have not provided clear or sustained evidence of benefit on sleepiness [66, 67]. 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 [68-73]. KLS prevalence is estimated around 1-4 cases per million, 5% of which are familial [72]. The consensus criteria for KLS diagnosis include at least two 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 one of: 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 hrs 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 [74]. A striking apathy affects nearly all patients [68]. 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 [70]. 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 one or two 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 [75]. 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 [73].

Episodes last a median 13 days, occurring every 3-6 months on average [76]. However, the picture varies from short episodes (e.g., 7 days) occurring every month in young patients, to prolonged episodes longer than one month (in 1/3 of the patients) with mostly apathy and altered cognition [70, 72]. The frequency and duration of episodes is unpredictable, although patients with long episodes at KLS onset usually continue to have long episodes and longer disease duration [72]. 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 [68].

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 [68]. The same triggers can be found, although less frequently, for subsequent episodes [71]. 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 [68]. Rare patients have late relapses, sometimes after 10-15 years without episodes [68, 72].

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 second bursts of bisynchronous, generalized, moderate- to high-voltage 5- to 7-Hz waves [68]. 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) [69, 77], up to 18 hours or more in some reports. Sleep efficiency is decreased, with frequent awakenings, excess of stages N1 and N2 [77], decreased N3 sleep during the first half and decreased REM sleep during the second half of episodes [78]. 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 [76]. 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. Cerebrospinal fluid (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 four 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 [73, 79], 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 [70, 72]. However, when 124 patients with KLS had systematic cognitive assessment during asymptomatic periods, they showed lower logical reasoning and non-verbal intelligence quotient, slower speed of processing, reduced attention, and reduced retrieval strategies in episodic verbal memory compared to controls [80]. 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 non-verbal 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 [81]. 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, 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, de-inhibition) 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 bi-thalamic ischemia [82]. 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 [74, 82]. 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 [74]. Two additional 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 anti-epileptic medication during episodes. There is some evidence for a recurrent, localized inflammatory encephalitis, including mild localized encephalitis in three 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. [83-86]. However, no HLA association was reproduced in large series [70, 72], and serum cytokine levels were normal [87]. As for genetic hypotheses, although familial risk is low (1% per first-degree relative), 5% of cases have an affected family member [70]. There are, to date, 19 multiplex families containing two to six affected members and 4 pairs of monozygotic twins [88, 89]. Karyotyping was normal in 112 patients [89]. Exome sequencing in familial cases did not yield any specific gene (Mignot, personal communication). 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 [68]. 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), 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 1g/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 [90]. Forty percent of treated patients experienced a shortening of episode duration by at least one 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 [90]. 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 [91, 92]. All five 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 [70, 76, 83], and may increase the irritability of the patients. When psychotic symptoms are prominent, neuroleptics like risperidone seem to be helpful [70, 76]. 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 [93]. 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 12h after the drug intake), episodes completely stopped in 35% of patients on lithium (versus only 3% of the non-lithium group). Episodes were less frequent or less severe in another 45% of lithium-treated patients, with immediate relapses within two days when lithium was discontinued [93]. 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. Anti-epileptic mood stabilizers (e.g., valproate) seem less effective than lithium. In women with menstrual-associated KLS, estrogen-progesterone may be tried [94].

Although the studies discussed in this review can provide some guidance for the treatment of the non-narcoleptic 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.

Acknowledgements: 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.

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

References

1. Trotti LM. Waking up is the hardest thing I do all day: Sleep inertia and sleep drunkenness. Sleep Med Rev. 2016.

2. Maness C, Saini P, Bliwise DL, Olvera V, Rye DB, Trotti LM. Systemic exertion intolerance disease/chronic fatigue syndrome is common in sleep centre patients with hypersomnolence: A retrospective pilot study. J Sleep Res. 2018:e12689.

3. Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. J Sleep Res. 2010;19:525-34.

4. Miglis MG, Schneider L, Kim P, Cheung J, Trotti LM. Frequency and Severity of Autonomic Symptoms in Idiopathic Hypersomnia. J Clin Sleep Med. 2020.

5. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

6. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. Sleep. 2009;32:753-9.

7. Evangelista E, Lopez R, Barateau L, et al. Alternative diagnostic criteria for idiopathic hypersomnia: A 32-hour protocol. Ann Neurol. 2018;83:235-47.

8. Pizza F, Moghadam KK, Vandi S, et al. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. J Sleep Res. 2013;22:32-40.

9. Ohayon MM, Reynolds CF, 3rd, Dauvilliers Y. Excessive sleep duration and quality of life. Ann Neurol. 2013;73:785-94.

10. Rye DB, Bliwise DL, Parker K, et al. Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of GABAA Receptors. Sci Transl Med. 2012;4:161ra51.

11. Landzberg D, Trotti LM. Is Idiopathic Hypersomnia a Circadian Rhythm Disorder? Current Sleep Medicine Reports. 2019;5:201-6.

12. Boucetta S, Montplaisir J, Zadra A, et al. Altered Regional Cerebral Blood Flow in Idiopathic Hypersomnia. Sleep. 2017;40.

13. Pomares FB, Boucetta S, Lachapelle F, et al. Beyond sleepy: structural and functional changes of the default-mode network in idiopathic hypersomnia. Sleep. 2019.

14. Sforza E, Roche F, Barthelemy JC, Pichot V. Diurnal and nocturnal cardiovascular variability and heart rate arousal response in idiopathic hypersomnia. Sleep Med. 2016;24:131-6.

15. Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To Split or to Lump? Classifying the Central Disorders of Hypersomnolence. Sleep. 2020.

16. Murillo-Rodriguez E, Barciela Veras A, Barbosa Rocha N, Budde H, Machado S. An Overview of the Clinical Uses, Pharmacology, and Safety of Modafinil. ACS Chem Neurosci. 2018;9:151-8.

17. Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time-a randomized, double-blind, placebo-controlled study. J Sleep Res. 2015;24:74-81.

18. Philip P, Chaufton C, Taillard J, et al. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep. 2014;37:483-7.

19. Sagaspe P, Micoulaud-Franchi JA, Coste O, et al. Maintenance of Wakefulness Test, real and simulated driving in patients with narcolepsy/hypersomnia. Sleep Med. 2019;55:1-5.

20. Inoue Y, Hirata K. The effectiveness of modafinil for the treatment of idiopathic hypersomnia. Sleep. 2017;40:A250-A1.

21. Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. Progress in neuro-psychopharmacology & biological psychiatry. 1988;12:695-700.

22. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep. 2007;30:1274-81.

23. Ali M, Auger RR, Slocumb NL, Morgenthaler T. Idiopathic hypersomnia: clinical features and response to treatment. J Clin Sleep Med. 2009;5:562-8.

24. Lavault S, Dauvilliers Y, Drouot X, et al. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. Sleep Med. 2011;12:550-6.

25. Schwartz JR, Feldman NT, Bogan RK. Dose effects of modafinil in sustaining wakefulness in narcolepsy patients with residual evening sleepiness. The Journal of neuropsychiatry and clinical neurosciences. 2005;17:405-12.

26. Modafinil package insert. 2004; Available from: https://www.modafinil.com/prescribe/index.html.

27. Reymond D. Alertec (modafinil) and the risk of congenital anomalies. Government of Canada/Health Canada; 2019 [10/30/2019]; Available from: https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/70201a-eng.php.

28. Damkier P, Broe A. First-Trimester Pregnancy Exposure to Modafinil and Risk of Congenital Malformations. JAMA. 2020;323:374-6.

29. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30:1705-11.

30. Adderall package insert. 2007; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/011522s040lbl.pdf.

31. Sunosi (solriamfetol) package insert. 2019; Available from: https://sunosihcp.com.

32. Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2019;199:1421-31.

33. Thorpy MJ, Shapiro C, Mayer G, et al. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. Ann Neurol. 2019;85:359-70.

34. Leu-Semenescu S, Nittur N, Golmard JL, Arnulf I. Effects of pitolisant, a histamine H3 inverse agonist, in drug-resistant idiopathic and symptomatic hypersomnia: a chart review. Sleep Med. 2014;15:681-7.

35. Wakix (pitolisant) package insert. 2019; Available from: https://wakix.com.

36. Bichler EK, Elder CC, Garcia PS. Clarithromycin increases neuronal excitability in CA3 pyramidal neurons through a reduction in GABAergic signaling. J Neurophysiol. 2017;117:93-103.

37. Garcia PS, Jenkins A, editors. Inhibition of the GABA(A) receptor by a macrolide but not by a lincosamide antibiotic. Proceedings of the 2009 Annual Meeting of the American Society of Anesthesiologists 2009.

38. Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in gamma-aminobutyric acid-Related hypersomnolence: A randomized, crossover trial. Ann Neurol. 2015;78:454-65.

39. Winkel P, Hilden J, Hansen JF, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10years in the CLARICOR randomised, blinded clinical trial. Int J Cardiol. 2015;182:459-65.

40. Clarithromycin Full Prescribing Information (package insert). Updated 1/2019.

41. Trotti LM, Saini P, Koola C, LaBarbera V, Bliwise DL, Rye DB. Flumazenil for the Treatment of Refractory Hypersomnolence: Clinical Experience with 153 Patients. J Clin Sleep Med. 2016;12:1389-94.

42. Kelty E, Martyn V, O'Neil G, Hulse G. Use of subcutaneous flumazenil preparations for the treatment of idiopathic hypersomnia: A case report. J Psychopharmacol. 2014.

43. Takei Y, Komada Y, Namba K, et al. Differences in findings of nocturnal polysomnography and multiple sleep latency test between narcolepsy and idiopathic hypersomnia. Clin Neurophysiol. 2012;123:137-41.

44. Tassi P, Muzet A. Sleep inertia. Sleep Med Rev. 2000;4:341-53.

45. Leu-Semenescu S, Louis P, Arnulf I. Benefits and risk of sodium oxybate in idiopathic hypersomnia versus narcolepsy type 1: a chart review. Sleep Med. 2016;17:38-44.

46. Vernet C, Arnulf I. Narcolepsy with long sleep time: a specific entity? Sleep. 2009;32:1229-35.

47. Thomann J, Baumann CR, Landolt HP, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. J Clin Sleep Med. 2014;10:1019-24.

48. Ramm M, Boentert M, Lojewsky N, Jafarpour A, Young P, Heidbreder A. Disease-specific attention impairment in disorders of chronic excessive daytime sleepiness. Sleep Med. 2018;53:133-40.

49. Arnulf I. Excessive daytime sleepiness and parkinsonism. Sleep Med Rev. 2005;9:185-200.

50. Ghergan A, Coupaye M, Leu-Semenescu S, et al. Prevalence and Phenotype of Sleep Disorders in 60 Adults With Prader-Willi Syndrome. Sleep. 2017;40:doi: 10.1093/sleep/zsx162.

51. Pépin J, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. Eur Resp J. 2009;33:1062-7.

52. Vernet C, Redolfi S, Attali V, et al. Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms. Eur Respir J. 2011;38:98-105.

53. Imbach LL, Valko PO, Li T, et al. Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. Brain. 2015;138:726-35.

54. Valko PO, Gavrilov YV, Yamamoto M, et al. Damage to histaminergic tuberomammillary neurons and other hypothalamic neurons with traumatic brain injury. Annals of neurology. 2015;77:177-82.

55. Sheng P, Hou L, Wang X, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. PLoS One. 2013;8:e81802.

56. Trotti LM, Bliwise DL. Treatment of the sleep disorders associated with Parkinson's disease. Neurotherapeutics. 2014;11:68-77.

57. Buchele F, Hackius M, Schreglmann SR, et al. Sodium Oxybate for Excessive Daytime Sleepiness and Sleep Disturbance in Parkinson Disease: A Randomized Clinical Trial. JAMA neurology. 2018;75:114-8.

58. Kaiser PR, Valko PO, Werth E, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. Neurology. 2010;75:1780-5.

59. Jha A, Weintraub A, Allshouse A, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. J Head Trauma Rehabil. 2008;23:52-63.

60. Menn SJ, Yang R, Lankford A. Armodafinil for the treatment of excessive sleepiness associated with mild or moderate closed traumatic brain injury: a 12-week, randomized, double-blind study followed by a 12-month open-label extension. J Clin Sleep Med. 2014;10:1181-91.

61. Annane D, Moore DH, Barnes PR, Miller RG. Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. Cochrane Database Syst Rev. 2006:CD003218.

62. Plante DT. Sleep propensity in psychiatric hypersomnolence: A systematic review and meta-analysis of multiple sleep latency test findings. Sleep Med Rev. 2017;31:48-57.

63. Vgontzas AN, Bixler EO, Kales A, Criley C, Vela-Bueno A. Differences in nocturnal and daytime sleep between primary and psychiatric hypersomnia: diagnostic and treatment implications. Psychosom Med. 2000;62:220-6.

64. Plante DT, Cook JD, Goldstein MR. Objective measures of sleep duration and continuity in major depressive disorder with comorbid hypersomnolence: a primary investigation with contiguous systematic review and meta-analysis. J Sleep Res. 2017;26:255-65.

65. Plante DT, Birn RM, Walsh EC, Hoks RM, Cornejo MD, Abercrombie HC. Reduced resting-state thalamostriatal functional connectivity is associated with excessive daytime sleepiness in persons with and without depressive disorders. J Affect Disord. 2018;227:517-20.

66. Dunlop BW, Crits-Christoph P, Evans DL, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. Journal of clinical psychopharmacology. 2007;27:614-9.

67. DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR, Modafinil in Depression Study G. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major

depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry. 2003;64:1057-64.

68. Arnulf I, Rico T, Mignot E. Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol. 2012;11:918-28.

69. Dauvilliers Y, Mayer G, Lecendreux M, et al. Kleine-Levin syndrome: an autoimmune hypothesis based on clinical and genetic analyses. Neurology. 2002;59:1739-45.

70. Arnulf I, Lin L, Gadoth N, et al. Kleine-Levin syndrome: a systematic study of 108 patients. Ann Neurol. 2008;63:482-93.

71. Huang Y, Guilleminault C, Lin K, Hwang F, Liu F, Kung Y. Relationship between Kleine-Levin Syndrome and upper respiratory Infection in Taiwan. Sleep. 2012;35:123-9.

72. Lavault S, Golmard J, Groos E, et al. Kleine-Levin syndrome in 120 patients: Differential diagnosis and long episodes. Annals of neurology. 2015;77:529-40.

73. Wang JY, Han F, Dong SX, et al. Cerebrospinal fluid orexin A levels and autonomic function in Kleine-Levin syndrome. Sleep. 2016;39:855-60.

74. Kas A, Lavault S, Habert MO, Arnulf I. Feeling unreal: a functional imaging study in 41 patients with Kleine-Levin syndrome. Brain. 2014;137:2077-87.

75. Hegarty A, Merriam AE. Autonomic events in Kleine-Levin syndrome. Am J Psychiatry. 1990;147:951-2.

76. Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine-Levin syndrome: a systematic review of 186 cases in the literature. Brain. 2005;128:2763-76.

77. Gadoth N, Kesler A, Vainstein G, Peled R, Lavie P. Clinical and polysomnographic characteristics of 34 patients with Kleine-Levin syndrome. J Sleep Res. 2001;10:337-41.

78. Huang Y, Lin Y, Guilleminault C. Polysomnography in Kleine-Levin syndrome. Neurology. 2008;70:795-801.

79. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol. 2002;59:1553-62.

80. Uguccioni G, Lavault S, Chaumereuil C, Golmard JL, Gagnon JF, Arnulf I. Long-term cognitive impairment in Kleine-Levin syndrome. Sleep. 2015;39:429-38.

81. Groos E, Chaumereuil C, Flamand M, et al. Emerging psychiatric disorders in Kleine-Levin syndrome. J Sleep Res. 2018;27:e12690.

82. Huang YS, Guilleminault C, Kao PF, Liu FY. SPECT findings in the Kleine-Levin syndrome. Sleep. 2005;28:955-60.

83. Carpenter S, Yassa R, Ochs R. A pathologic basis for Kleine-Levin syndrome. Arch Neurol. 1982;39:25-8.

84. Koerber RK, Torkelson R, Haven G, Donaldson J, Cohen SM, Case M. Increased cerebrospinal fluid 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in Kleine-Levin syndrome. Neurology. 1984;34:1597-600.

85. Takrani LB, Cronin D. Kleine-Levin syndrome in a female patient. Can Psychiatr Assoc J. 1976;21:315-8.

86. Fenzi F, Simonati A, Crosato F, Ghersini L, Rizzuto N. Clinical features of Kleine-Levin syndrome with localized encephalitis. Neuropediatrics. 1993;24:292-5.

87. Kornum B, Rico T, Lin L, et al. Serum cytokine levels in Kleine-Levin syndrome. Sleep medicine. 2015;16:961-5.

88. Bahammam A, Gadelrab M, Owais S, Alswat K, Hamam K. Clinical characteristics and HLA typing of a family with Kleine-Levin syndrome. Sleep medicine. 2008;9:575-8.

89. Nguyen Q, Groos E, Leclair-Visonneau L, et al. Familial Kleine-Levin syndrome. Sleep. 2016;39:1535-42.

90. Leotard A, Groos E, Chaumereuil C, et al. IV steroids during long episodes of Kleine-Levin syndrome. Neurology. 2018;90:e1488-e92.

91. Rezvanian E, Watson NF. Kleine-levin syndrome treated with clarithromycin. J Clin Sleep Med. 2013;9:1211-2.

92. Trotti LM, Bliwise DL, Rye DB. Further Experience using Clarithromycin in Patients with Kleine-Levin Syndrome. J Clin Sleep Med. 2014;10:457-8.

93. Leu-Semenescu S, Le Corvec T, Groos E, Lavault S, Golmard JL, Arnulf I. Lithium therapy in Kleine-Levin syndrome: an open-label, controlled study in 130 patients. Neurology. 2015;85:1655-62.

94. Billiard M, Guilleminault C, Dement WC. A menstruation-linked periodic hypersomnia. Kleine-Levin syndrome or new clinical entity? Neurology. 1975;25:436-43.