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Review Article

Idiopathic Hypersomnia and Hypersomnolence Disorder: A Systematic Review of the Literature

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Background: *Hypersomnia is a common complaint in medical offices. Often patients are given psychiatric diagnoses, but a primary sleep disorder may be present. The new diagnosis of "hypersomnolence disorder" (HD) in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition is a primary sleep disorder most similar to the diagnosis "idiopathic hypersomnia" (IH) in sleep literature and can be missed in psychiatric settings.* **Methods:** *A systematic review of the computerized databases PubMed, EMBASE, Web of Science, and Psychinfo using the search criteria "idiopathic AND (hypersomnolence OR hypersomnia)," as well as "hypersomnolence disorder was conducted." Articles were included if they were in English and included information regarding the epidemiology, diagnosis, pathophysiology, or treatment of IH or HD. Where relevant, weighted means and 95% CI were calculated based on the number of subjects in each study.* **Results:** *A total of 143 articles discussed IH, whereas no articles were found regarding HD. Most articles were review articles, prospective studies, or studies of pathophysiology. IH is found in approximately 0.02%–0.010% of the general population, has a mean age of onset of 21.8 years, and is associated with several somatic symptoms. Alterations in histaminergic or dopaminergic signaling may be involved in IH. Treatment with modafinil or other stimulants appears moderately effective. IH can be differentiated from psychiatric hypersomnolence by formal polysomnography.* **Conclusions:** *IH and HD are relatively uncommon disorders and little is known about them. However, they are distinct from psychiatric disorders and respond well to treatment once properly identified.*

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INTRODUCTION

Difficulty with sleep is a common complaint in many psychiatric offices. Patients with major depressive disorder can demonstrate variable changes in their sleep patterns, including initial, middle, or late insomnia or hypersomnia. These can be some of the most disturbing and debilitating symptoms for these patients and are often a target of treatment. Insomnia is more common than hypersomnia for most patients with depression, although estimates of the prevalence of hypersomnia in patients with depression range from 9%–26%.[1,2] When present, hypersomnia can result in inability to initiate or maintain employment, difficulty in self-care, difficulty in child care or caring for elderly family members, and loss of social interaction and isolation.

Hypersomnia (also called excessive daytime sleepiness [EDS]) has a broad differential diagnosis.

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Unfortunately, there is no diagnostic consensus between psychiatric definitions of disorders of hypersomnolence (as outlined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition[3]) and neurologic definitions of these same conditions (as outlined in the International Classification of Sleep Disorders, third edition[4]), although similar diagnoses are present between the 2 diagnostic systems (Table 1). Evaluation of patients who present with hypersomnia should begin with a careful history and elimination of potential medical causes for their symptoms. Important topics of consideration include a thorough medical history, especially focusing on conditions that could lead to fatigue and sedation; medication history (including supplements and over-the-counter medications); and a thorough description of the patient's sleep habits. Treatment of EDS is dependent on the underlying etiology and may include pharmacologic (stimulants, thyroid hormone, antidepressants, reduction in sedating medications), physiologic (continuous positive airway pressure or bilateral positive airway pressure), and behavioral (sleep hygiene techniques, cognitive-behavioral therapy, substance abuse treatment) approaches. For a more thorough overview of EDS evaluation and treatment, see a recent review.[5]

The diagnosis of "Hypersomnolence Disorder" (HD) is recognized as a primary sleep-wake disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition.[3] Diagnostic criteria for the disorder include excessive subjective sleepiness despite periods of extended sleep (>9 h/d) that is nonrestorative, or recurrent periods of sleep lapses in the day or both, or difficulty being fully awake after abrupt awakening (sleep drunkenness). The hypersomnolence must have occurred for greater than 3 months and result in functional impairment. The diagnosis of HD is not recognized by the American Academy of Sleep Medicine in the International Classification of Sleep Disorders, third edition. Most literature in the field of sleep medicine identifies "idiopathic hypersomnia" (IH) or "idiopathic hypersomnolence" as a distinct diagnosis, rather than "Hypersomnolence Disorder." Diagnostic criteria for IH as outlined by the American Academy of Sleep Medicine are similar to those of

TABLE 1. Differential Diagnosis of Excessive Daytime Sleepiness, Separated by Diagnostic Manual

ICSD-3 Diagnoses	DSM-5 Diagnoses	
Hypersomnias of central origin	*Hypersomnias*	
Behaviorally-induced insufficient sleep syndrome	Other specified hypersomnolence disorder	
Idiopathic hypersomnia	Hypersomnolence disorder	
Narcolepsy with or without cataplexy	Narcolepsy	
Narcolepsy caused by a medical disorder		
Recurrent hypersomnia, Kleine-Levin syndrome	Other specified hypersomnolence disorder	
Recurrent hypersomnia, menstrual-related	Other specified hypersomnolence disorder	
Sleep-related breathing disorders	*Sleep-related breathing disorders*	
Obstructive sleep apnea	Obstructive sleep apnea hypopnea	
	Central sleep apnea	
	Sleep-related hypoventilation	
Hypersomnia due to drug or substance	*Substance/medication-induced sleep disorder*	
Alcohol	Antihistamines	Dopaminergic medications
Antidepressants	Antihypertensives	Hypnotics
Antiepileptics	Antipsychotics	Opiates
Other		
Long sleeper	Unspecified hypersomnolence disorder	
Hypersomnia caused by a medical condition (not specific to ICSD-3 or DSM-5)		
Brain tumors	Hypothyroidism	Posttraumatic hypersomnia
Depression	Infections (or postinfection)	Toxic/metabolic
Dementia	Parkinson disease	Restless leg syndrome
Genetic disorders		

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ICSD-3 = International Classification of Sleep Disorders, third edition.

HD, but differ in the inclusion of several objective findings on formal diagnostic testing.[4] These include a mean sleep latency on the multiple sleep latency test (MSLT) of $\leq$8 min or the 24-h total sleep time of $\geq$660 min on polysomnographic monitoring or wrist actigraphy. In addition, there must be $<$2 sleep-onset rapid eye movement periods during the MSLT, and cataplexy must be absent. What is fundamental to both diagnoses is the presence of excessive sleepiness despite adequate sleep time at night in the absence of other factors that could contribute to daytime sedation. Given that HD is a new diagnosis, most of the information used in constructing this diagnosis draws on studies of individuals with the diagnosis of IH.[3] In order to more fully understand the current state of knowledge regarding HD, a systematic review of the literature was conducted.

METHODS

A systematic search for studies was conducted on IH or HD. The computerized databases of PubMed, EMBASE, Web of Science, and Psychinfo were searched for studies published from earliest entry date in the database through September 2015. The search criteria "idiopathic AND (hypersomnolence OR hypersomnia)," as well as "hypersomnolence disorder" in each database and also hand-searched in reference sections of relevant articles were used. Articles were included if they were in English and included information regarding the epidemiology, diagnosis, pathophysiology, treatment, or prognosis of IH or HD. Articles not meeting these search criteria were excluded. Editorials, review articles, and abstracts from meetings were included in the search results, given that the number of search hits was small and the desire to have a full understanding of the current state of knowledge in the field. The titles of all studies identified from the search were examined, and studies that clearly did not pertain to the topic of interest were eliminated. Studies that were deemed potentially pertinent based on their titles had their abstracts examined. Studies clearly not meeting our inclusion criteria based on their abstracts were eliminated from further review. The full-text articles of the remaining studies were examined for inclusion, and data extraction was conducted if deemed appropriate. From the included studies, information was extracted, including study type, number of participants, measurements made, and outcomes where appropriate. All articles meeting the inclusion criteria were included, regardless of the quality of the study. Where relevant, weighted means were calculated based on the number of subjects in each study and 95% CI were calculated using Microsoft Excel. In order to assess variability in the data between studies, interquartile ranges (IQR) were calculated where relevant using Microsoft Excel.

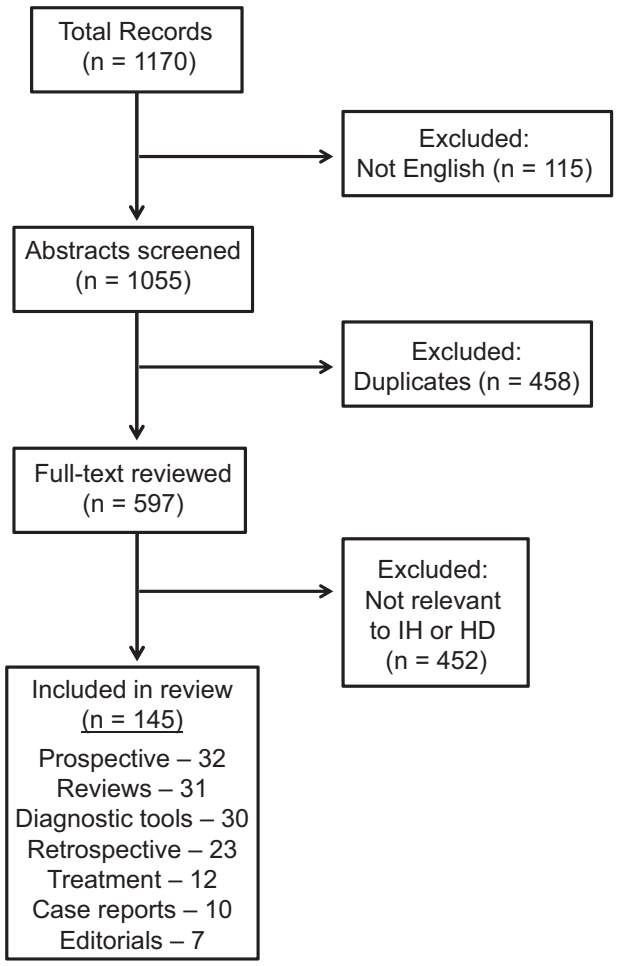
RESULTS AND DISCUSSION

A total of 1170 unique records pertaining to IH were found in the literature (Figure). There were no articles identified discussing the newer diagnosis of "Hypersomnolence Disorder." A total of 145 articles met the inclusion criteria, with the majority being prospective studies, review articles, and studies of diagnostic tools. Later, the key findings from the literature were summarized regarding the epidemiology, sleep characteristics, pathophysiology, and treatment of IH.

Epidemiology

Summary of the published data on the epidemiology of IH is shown in Table 2. There are currently no clear systematic studies of the prevalence of IH in the general population. Estimates are derived from comparisons in the prevalence of IH to those of narcolepsy in sleep medicine populations (16 cases of IH per 100 cases of narcolepsy).[6] In 5 studies of patients referred for evaluation of EDS, the prevalence of IH in these populations varies from 10.3%–28.5%.[7–11] One cross-sectional study evaluated the prevalence of IH in an inpatient general hospital ward and showed it to be present in just 2 (0.08%)of 2518 patients.[12] Overall, the most common consensus in the literature is a prevalence around 0.002%–0.010%.[6,13–15] There does not appear to be a difference in prevalence between men and women, although published data are limited. The mean age of onset is 21.9 years (95% CI: 21.5–22.2; IQR = 1.9 [20.5–22.4]),[16–21] although diagnosis may be several years after the onset of symptoms.[6,13–15,22–24] Approximately 29.4% (95% CI: 28.3–30.6; IQR = 8.6 [31.5%–40.1%]) of patients with IH report a family history of the condition,[8,21,23,24] suggesting a possible genetic component to the etiology of IH. Although the HLA-DQB1*0602 allele is present in up to 95% of individuals diagnosed with narcolepsy with cataplexy,[25] the weighted mean prevalence of the allele in 888

FIGURE. Diagram of the systematic review of studies on idiopathic hypersomnia (IH) or hypersomnolence disorder (HD).



individuals with IH is 21.3% (95% CI: 20.4–22.2; IQR = 17.6 [15.9%–33.5%]),[18–20,23,26–41] which is close to the prevalence rate seen in general populations.[25] IH is associated with several somatic symptoms and comorbid conditions (Table 2). Memory difficulties (79%),[42] attentional difficulties (55%),[42] chronic headache (52.8%),[8,43] and excessive sweating (34.7%)[8,43] are particularly prominent. Depression is present in 15.1% of patients (95% CI: 14.3–15.9; IQR = 4.3 [15.7%–20.0%]).[8,29,44]

Sleep Characteristics and Impairment of Function

Search results regarding sleep characteristics of patients with IH are summarized in Table 2. Individuals with IH are profoundly sleepy, as shown by the weighted mean value for the Epworth Sleepiness Scale (ESS) of 15.9 (95% CI: 15.8–16.1; IQR = 2 [15%–17%]) [18–20,29,40,42,45–48] Their sleepiness interferes with normal daily activities, including occupational and social functioning. Nocturnal sleep and naps tend to be long and unrefreshing.[13,16,49] Most patients with IH do not have sleep paralysis (20.8%, 95% CI: 19.7–21.8; IQR = 16.9 [11.1%–28.0%])[6,17,21,23,24,27,29,38,40,50] or hypnagogic hallucinations (20.0%, 95% CI: 18.9–21.2; IQR = 17.9 [8.9%–26.8%]).[17,21,23,24,27,29,38,40,51] Approximately half of them (50.9%, 95% CI: 48.8–53.1; IQR = 26.1 (35.7–61.8]) experience sleep drunkenness,[6,8,21,23,24,27,42] where a person remains in a confused state for a prolonged period of time upon awakening. On polysomnography, patients with IH show shortened sleep latency, increased total sleep time, and increased time in bed.[23,36,52] The weighted mean total sleep time for patients with IH is 538 min (95% CI: 526–549 min; IQR = 199 [461–660 min]),[2,19,21,24,27,40–42,47,48,52–56] although there is a wide variation in total sleep time between studies. MSLT values are abnormally short in patients with IH (weighted mean = 5.86 min, 95% CI: 5.76–5.96 min; IQR = 2.28 [4.62–6.90 min]),[2,6,9,17,21–24,30,33,36,38,40–42,47,48,52,57–65] although this is unsurprising given that this is part of the diagnostic criteria.[4] Most individuals with IH have relatively normal sleep architecture, although abnormal findings reported in the literature include a higher number of sleep spindles [66] and higher sleep spindle index, suggesting a higher arousal threshold and weakened awakening mechanism[53]; a greater number of REM sleep interruptions[41] and increased REM density,[9] suggesting poor sleep satiety; and decreased slow wave activity.[64] Studies examining the consequences of altered sleep on function in patients with IH show impaired functioning on sustained attention tasks,[67] decreased psychomotor vigilance with increased cognitive lapses,[45] and cognitive impairment on the forced awakening test.[61,68,69] In addition, quality-of-life measures in cohorts of patients with IH show lower quality-of-life scores in essentially all domains compared with healthy controls, with the exception of physical function and physical pain.[60,70–72]

Pathophysiology of IH

Several studies have examined changes in neurotransmitter signaling and neuronal functioning that might contribute to the development of IH. Many focused on the neuropeptide hypocretin-1 (orexin),

TABLE 2. Epidemiologic Factors Involving Sleep Characteristics and Comorbid Conditions of Idiopathic Hypersomnia, From Systematic Review of the Literature

	Total *N*	Mean	95% CI	IQR(25–75)
Age of onset	245	21.8 y	21.5–22.2 y	1.9 (20.5–22.4) y
Family history	323	29.4%	28.3%–30.6%	8.6 (31.5–40.1)%
HLA-DQB1*0602 positivity	874	20.9%	20.1%–21.8%	17.6 (15.9–33.5)%
ESS	468	15.9	15.8–16.1	2 (15–17)
Sleep paralysis	530	20.8%	19.7%–21.8%	16.9 (11.1–28.0)%
Hypnagogic hallucinations	519	20.0%	18.9%–21.2%	17.9 (8.9–26.8)%
Sleep drunkenness	538	50.9%	48.8%–53.1%	26.1 (35.7–61.8)%
Total sleep time	514	538 min	526–549 min	199 (461–660) min
MSLT	1057	5.86 min	5.76–5.96 min	2.28 (4.63–6.90) min
Comorbid symptoms				
Memory	62	79%	N/A	N/A
Attention	62	55%	N/A	N/A
Temp regulation	62	25%	N/A	N/A
Feeling faint	98	32.5%	31.2%–33.8%	6.3 (31.5–37.8)%
Digestive	62	22%	N/A	N/A
Palpitation	62	23%	N/A	N/A
Raynaud	60	24.6%	24.4–24.7%	N/A
Excessive sweating	36	34.7%	28.3–41.1%	N/A
Orthostasis	29	42.9%	N/A	N/A
Headache	36	52.8%	43.3–62.2%	N/A
Depression	235	15.1%	14.3–15.9%	4.3 (15.7–20.0)%

ESS = Epworth sleepiness scale; IQR = interquartile range; MSLT = mean sleep latency test; *N* = number; N/A = not applicable.

which is involved in wakefulness, arousal, and appetite, and is decreased in the cerebrospinal fluid (CSF) of individuals with narcolepsy with cataplexy.[17,28,31,33,34,62,73] However, 8 studies on a total of 96 patients with IH found that CSF hypocretin-1 levels in patients with IH do not differ from controls.[17,28,31–34,62,73] Others have measured histamine, which is known to be involved in the promotion of arousal and wakefulness. CSF histamine levels are higher during wakefulness and ablation of histaminergic signaling leads to decreased wakefulness in animal models.[74,75] A total of 2 studies found that CSF histamine was decreased in patients with IH compared with controls,[34,73] whereas 1 study found no difference.[17] One of the studies that found decreased CSF histamine in patients with IH showed an increase in levels back toward the normal range with stimulant treatment.[34] One study measured CSF levels of the serotonin metabolites homovanillic acid and 5-hydroxyindoleacetic acid in a single patient with IH and found them to be lower compared with a control group.[76] However, it is difficult to speculate on the significance of these results from this lone case. A study examined dopamine signaling in the brains of patients with IH using positron emission tomography.[57] It showed increased dopamine receptor availability in the putamen and caudate and increased dopamine uptake in the putamen. This suggests
that there is dysfunctional dopamine transmission in patients with IH, with possible deficient synaptic dopamine release. Finally, recent work shows that CSF from patients with IH can enhance signaling through γ-aminobutyric acid A receptors ($GABA_ARs$), which are known to dampen consciousness and regulate sleep.[77] The study suggests that there is a naturally occurring positive allosteric modulator of $GABA_ARs$ in the CSF of patients with IH that may contribute to their decreased level of arousal.

In addition to neuronal signaling, some have examined potential differences in gene regulation in IH. One group examined the possible role of microRNAs in the pathogenesis of IH. MicroRNAs are posttranscriptional regulators of gene expression, and there is evidence that they are involved in neurodegenerative diseases.[78] Analysis of microRNAs profiles from serum of patients with IH revealed 6 possible candidates that were different from controls.[32] However, in a subsequent analysis of CSF from patients with IH and controls, there were no significantly

different microRNAs between the 2 groups.[79] One study examined gene regulation of circadian clock core components in individuals with IH to see if the dynamics of the circadian network are altered.[59] It showed a significant reduction in the expression of key transcription factors from the molecular clock system in cultured dermal fibroblasts from patients with IH. This altered expression pattern could contribute to the pathogenesis of the condition, although further studies using neurons *in vitro* or *in situ* would provide stronger evidence for altered circadian clock regulation in the brains of patients with IH.

Finally, to investigate whether an autoimmune process is involved in the etiology of IH, a study examined the levels of immunoglobulins (Ig) from the serum of patients with IH compared with controls and patients with narcolepsy.[80] It showed that patients with IH had elevated serum total IgG, IgG3, and IgG4 levels, a higher IgG1/IgG2 ratio, and a decreased IgG2 level compared with both controls and patients with narcolepsy. Although these results suggest that patients with IH have alterations in their immune system, it is unclear if these are related to the etiology of the condition or the result of the effects of altered sleep on immune expression.[81]

Treatment

Few studies have been conducted on the treatment of IH, and those that do exist are with a limited number of medications (Table 3). Modafinil is the most studied treatment, with a total of 8 studies examining the effects of it alone or in combination with another stimulant.[18,23,24,46,54,69,82,83] It is the only treatment for IH that has been studied in randomized control trials. One randomized control trial showed that treatment of patients with IH with modafinil improved performance on a driving test.[83] The other randomized control trial examined the response to modafinil treatment in patients with IH compared with placebo as determined by a reduction in ESS to ≤ 10.[46] Using this criterion, 71% of individuals with IH responded to modafinil treatment, and 2 small, open-label trials of modafinil showed an improvement in drowsiness and a decrease in sleep episodes during the day,[82] as well as significantly lower P300 latencies in treated individuals, suggesting improved cognitive function.[69] In the largest study to date, prospective measures in 104 individuals with IH who were placed on modafinil by their providers showed that the treatment led to an average reduction in ESS by 2.6 points;[18] 2 moderate-sized retrospective chart reviews showed that approximately 44% of individuals on modafinil responded to treatment, with anywhere from 15%–50% of patients switching to a different medication.[23,24] The same 2 studies also showed that the addition of other stimulant medications to modafinil, such as caffeine or dextroamphetamine had variable results, with anywhere from 33%–100% of patients responding to treatment. However, the number of patients was very small. Finally, a small case report showed that 2 family members with IH treated with modafinil both showed good treatment response.[54] Given the predominance of studies using modafinil, which show moderate treatment effects with fair tolerability, most experts recommend modafinil as a first-line treatment for IH.[13,15,84,85]

Other than modafinil, other stimulant medications have been tried for the treatment of IH. Chart reviews show that with the exception of methylphenidate, the use of other stimulants is limited and has variable results.[23,24] In a study, the use of methylphenidate in 61 individuals showed a response in 62% of patients, with 34% switching to another medication.[24] Review of 37 patients treated with the non-amphetamine stimulant mazindol showed that this medication was well tolerated (11% adverse events) and fairly efficacious (mean reduction in ESS of 4.8 points).[20]

A total of 4 non–stimulant-based treatments for IH have been studied. A case report and one small, open-label trial showed that treatment with low-dose levothyroxine is well tolerated and resulted in dramatic improvements in ESS (12.5 and 10.4 point reductions in ESS).[47,56] A moderate-sized retrospective review of the use of pitolisant, an inverse agonist of the H3 histamine autoreceptor, showed this medication to be well tolerated (28% adverse events), but not particularly efficacious, as only 35% of treated individuals responded and the mean reduction in ESS was 1.5.[19] An editorial comment described how treatment of 10 individuals with IH with melatonin resulted in decreased nocturnal sleep duration, decreased daytime sleepiness, and decreased sleep drunkenness.[86] However, these data have not been formally published. A case report of treatment of an individual with the

TABLE 3. Summary of Studies of the Treatment of Idiopathic Hypersomnia

Study	Total N	Type of study	Treatment	Responders	Switched Med	Added Med	Reduction in ESS	Outcome Measure	Outcome	AEs
Ali et al.[24]	50	Retrospective chart review	Modafinil	22 (44%)	25	0	–	Complete or partial response (subjective)		
Anderson et al.[23]	54	Retrospective chart review	Modafinil	24 (44%)	8	6	6	Response = drop in ESS $\geq$ 4 points		38.9%
Bastuji and Jouvet[82]	15	Open label	Modafinil	?	0	0	–	Sleep diary	Drowsiness improved Sleep episodes reduced	
Janackova et al.[54]	2	Case report	Modafinil	2 (100%)	0	0	–	Subjective response		
Lavault et al.[18]	104	Prospective monitoring	Modafinil	?	25	4	2.6	Change in ESS; patient report on visual analog scale; physician impression of change	Patient report of efficacy = 6.9/10 Physician imp.= 89% improvement	51.5%
Mayer et al.[46]	17	RCT	Modafinil	12 (71%)	N/A	N/A	7	Response = ESS $\leq$ 10; change in ESS; change in sleep latency in MWT	No change in latency in MWT	52.9%
Phillip et al.[83]	14	RCT	Modafinil	N/A	N/A	N/A	–	of inappropriate line crossings Standard deviation of lateral position on driving test	Sig fewer of ILCs and decreased SDLP in treated	
Yaman et al.[69]	18	Open label	Modafinil	?	N/A	N/A	–	P300 latencies	Sig lower P300 latencies with modafinil	
Ali et al.[24]	1	Retrospective chart review	Modafinil + Dextroamphetamine	1 (100%)	0	0	–	Complete or partial response (subjective)		
Anderson et al.[23]	3	Retrospective chart review	Modafinil + Dextroamphetamine	1 (33%)	0	0	–	Response = drop in ESS $\geq$ 4 points		
Anderson et al.[23]	3	Retrospective chart review	Modafinil + Caffeine	2 (67%)	0	0	–	Response = drop in ESS $\geq$4 points		
Ali et al.[24]	7	Retrospective chart review	Dextroamphetamine	0 (0%)	5	0	–	Complete or partial response (subjective)		
Anderson et al.[23]	8	Retrospective chart review	Dextroamphetamine	5 (63%)	0	0	–	Response = drop in ESS $\geq$4 points		
Ali et al.[24]	8	Retrospective chart review	Amphetamine-Dextroamphetamine	4 (50%)	4	0	–	Complete or partial response (subjective)		
Ali et al.[24]	5	Retrospective chart review	Methamphetamine	3 (60%)	2	0	–	Complete or partial response (subjective)		
Ali et al.[24]	7	Retrospective chart review	Pemoline	3 (43%)	4	0	–	Complete or partial response (subjective)		
Ali et al.[24]	1	Retrospective chart review	Caffeine	1 (100%)	0	0	–	Complete or partial response (subjective)		
Ali et al.[24]	61	Retrospective chart review	Methylphenidate	38 (62%)	21	0	–	Complete or partial response (subjective)		

Ali et al.[24]	1	Retrospective chart review	Methylphenidate + Dextroamphetamine	1 (100%)	0	0	–	Complete or partial response (subjective)		
Ali et al.[24]	2	Retrospective chart review	Methylphenidate + Amphetamine-Dextroamphetamine	2	0	0	–	Complete or partial response (subjective)		
Ali et al.[24]	1	Retrospective chart review	Methylphenidate + Sodium oxybate	0	0	0	–	Complete or partial response (subjective)		
Shinno et al.[56]	2	Case report	Levothyroxine	2 (100%)	0	0	12.5	Daily total sleep time and change in ESS		
Shinno et al.[46]	9	Open label	Levothyroxine	9 (100%)	0	0	10.4	Daily total sleep time and change in ESS		0%
Nittur et al.[20]	37	Retrospective chart review	Mazindol	?	6	3	4.8	Change in ESS		11%
Kelty et al.[87]	1	Case report	Flumazenil	1 (100%)	0	0	–	Change in ESS, SSS, CIWA		
Leu-Semenescu et al.[19]	65	Retrospective chart review	Pitolisant	23 (35%)	34	11	1.5	Subjective response and change in ESS		28%
Montplaisir and Fantini[86]	10	Unpublished case series	Melatonin	5 (50%)	?	?	–	Sleep duration, daytime sleepiness	Decreased nocturnal sleep duration, decreased daytime sleepiness	
Trotti et al.[88]	20	RCT	Clarithromycin	–	–	–	4.0	PVT performance, ESS	No difference in PVT; decreased subjective sleepiness	95%

AE = adverse event; CIWA = Clinical Institute Withdrawal Assessment; ESS = Epworth Sleepiness Scale; ILC = inappropriate line crossing; MWT = Maintenance of Wakefulness Test; PVT = Psychomotor Vigilance Test; RCT = randomized control trial; SDLP = standard deviation of lateral position; SSS = Stanford Sleepiness Scale.

? = Unable to determine from study manuscript.

GABA receptor antagonist flumazenil suggested that this medication could potentially decrease ESS significantly in patients with IH.[87] Finally, a recent randomized, double-blind, placebo-controlled trial studied the effect of clarithromycin, a $GABA_AR$-negative allosteric modulator, on psychomotor vigilance and subjective sleepiness in patients with "GABA-related hypersomnia," which included IH and narcolepsy without cataplexy.[88] This work was based on the observations described earlier regarding a possible naturally occurring positive allosteric inhibitor present in the CSF of patients with IH.[77] Clarithromycin did not affect psychomotor vigilance, but did improve subjective daytime sleepiness (reduction in ESS of 4.0). Although the reported adverse effect rate was high (95%), most of these were minor symptoms, and the adverse effect rate in the placebo group was also quite high (75%), suggesting that clarithromycin is relatively well tolerated in this group.

In summary, modafinil is the most well-studied treatment and shows moderate efficacy. Other stimulants may be well tolerated and efficacious, but further dedicated studies are needed. Other treatments, such as levothyroxine, melatonin, flumazenil, and clarithromycin show promise, but require further studies. The H3 receptor inverse agonist pitolisant does not appear to be particularly effective in treating IH, although it is well tolerated.

Differentiating Hypersomnia Due to a Mental Disorder and IH or HD

As discussed earlier, perceived EDS and hypersomnia can be a common complaint to mental health providers. As outlined in a recent review, the assessment of EDS starts with a careful history and possible use of subjective patient-report scales.[5] Objective measures may then be necessary. Actigraphy can be helpful in identifying insomnia and insufficient sleep.[89] Polysomnography is useful to assess for sleep-disordered breathing and abnormal movements during sleep.[90] A study suggests that polysomnography may be useful in differentiating hypersomnia due to a mental disorder and IH, as they were able to document differences in several polysomnography measurements between the groups.[91] However, these differences may not be that useful in clinical practice and are not the gold standard objective measure of excessive sleepiness. This distinction goes to the MSLT, for which there are specific guidelines recommended by the American Academy of Sleep Medicine.[92] Individuals with IH or HD would have a shortened MSLT, whereas those with hypersomnia due to a mental disorder would typically have a normal MSLT. MSLT can also be used to differentiate narcolepsy from IH or HD. Thus, if there are concerns by the mental health provider of an underlying diagnosis of IH, referral to a sleep specialist to rule out other causes of EDS and to conduct definitive testing (MSLT) should be considered. More thorough descriptions of the evaluation of EDS for mental health providers are available elsewhere.[5,90]

SUMMARY AND CONCLUSION

In summary, IH is a relatively uncommon disorder, affecting $<1\%$ of the general population and approximately 10%–30% of patients with EDS. Available studies suggest that it has an early onset, may have a genetic component, and is associated with several somatic symptoms. Current research suggests that it is a disorder of hypoarousal, with several possible underlying changes in CNS neuronal signaling. However, the exact pathophysiology of the condition is largely unknown. Treatment with the stimulant modafinil has the most support in the literature, although other stimulants may be effective. Formal study by a sleep specialist to rule out other causes of EDS and to conduct definitive testing (MSLT) is recommended. It is important for clinicians to make the correct diagnosis to avoid undue stress to patients related to unremitting symptoms, as well as the potential adverse effects of ineffective treatments. Given that, the vast majority of patients with IH have a long duration between symptom onset and treatment, clinical vigilance is necessary to improve outcomes.

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