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ABSTRACT

Idiopathic hypersomnia is a central hypersomnolence disorder of unknown origin characterized by excessive daytime sleepiness despite normal or long sleep time, and frequent severe sleep inertia. Management strategies have been largely derived from expert consensus, due to a lack of disease-specific assessments and reliance on case series and rare randomized controlled studies. Guidelines recommend treatment with off-label medications. Modafinil, which was approved for idiopathic hypersomnia until 2011 in Europe, is the most commonly used treatment and improved sleepiness in two recent randomized placebo-controlled trials. In 2021, low-sodium oxybate (LXB) was approved in the United States for idiopathic hypersomnia. In a placebo-controlled, double-blind, randomized withdrawal study, LXB reduced daytime sleepiness and sleep inertia, and improved daily functioning. Here, treatment options are reviewed considering the authors' professional experience, current guidelines, and the latest research developments. The choice of pharmacotherapy should be guided by symptom profile, age, comorbidities (eg, depressive symptoms, cardiovascular problems), and concomitant medications (eg, oral contraceptives). Nonpharmacologic approaches have a role in management. An instrument (idiopathic hypersomnia severity scale) has been validated in idiopathic hypersomnia specifically, opening a path to better assessment of symptoms, impact, and response to treatment. Continued research on idiopathic hypersomnia is needed to support treatment algorithms.

1. Introduction

The most common central disorders of hypersomnolence are narcolepsy types 1 and 2, idiopathic hypersomnia, and Kleine-Levin syndrome. First recognized in the 1970s [1–3], idiopathic hypersomnia is a debilitating sleep disorder, with an estimated prevalence of one per 10,000 people [4]. Women are affected more frequently than men [5–7].

The core symptom of idiopathic hypersomnia is excessive daytime sleepiness (EDS), defined as an inability to stay awake and alert during the day, resulting in an irrepressible need to sleep or unplanned lapses into sleep or drowsiness [1,8,9]. Some patients experience sleep excess (≥11 h total in a 24-h period) and sleep inertia, which impact the ability to awaken properly on time [8]. Sleep inertia (often called "sleep drunkenness" when severe) refers to major difficulty awakening, typically after nocturnal sleep but also after naps, such that the patient requires several loud alarms or physical shaking and may still immediately return to sleep [8]. Confusion, slowness, lack of coordination, and aggressiveness may be present when the patient manages to rise [8]. Other symptoms include long (>60 min) and unrefreshing naps, and cognitive impairment (memory or attention deficits, "mental fog") [1,8–10]. The physical burden of idiopathic hypersomnia symptoms leads to diminished health-related quality of life, impaired functioning across multiple domains, poor work/school performance, and negative impacts on employment, income, and general health [8,11,12]. Several symptoms and features are shared between idiopathic hypersomnia and psychiatric disorders, including

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Abbreviations

AASM	American Academy of Sleep Medicine
AE	adverse event
CBT	cognitive behavioral therapy
CSF	cerebrospinal fluid
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
FOSQ	functional outcomes of sleep questionnaire
FOSQ-10	functional outcomes of sleep questionnaire, short version
GABA	gamma-aminobutyric acid
HSI	hypersomnia severity index
ICSD	*International Classification of Sleep Disorders*
IHSS	idiopathic hypersomnia severity scale
LST	long sleep time
LXB	low-sodium oxybate
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NREM	non−rapid eye movement
OSA	obstructive sleep apnea
PGIc	patient global impression of change
PVT	psychomotor vigilance task
RCT	randomized controlled trial
REM	rapid eye movement
SDP	stable-dose period
SIQ	sleep inertia questionnaire
SOREMP	sleep onset REM period
SXB	sodium oxybate
TEAE	treatment-emergent adverse event
US,	United States
VAS-SI	visual analog scale for sleep inertia
WPAI:SHP	work productivity and activity impairment questionnaire: specific health problem

hypersomnia, anxiety, depression, cognitive/attentional deficits, and social/occupational impairment [8,13−15], potentially contributing to misdiagnosis or delayed diagnosis in many patients [5,13,16]. Clinical considerations in the diagnosis of idiopathic hypersomnia are discussed in detail elsewhere [17].

The *International Classification of Sleep Disorders*, second edition (ICSD-2) distinguished idiopathic hypersomnia with long sleep time (LST; >10 h nocturnal sleep) and without LST (>6 h and <10 h nocturnal sleep) [18]. This distinction was omitted from the third edition (ICSD-3) because differentiating clinical and/or polysomnographic characteristics could not be defined [8,19], although this is controversial [20]. As the multiple sleep latency test (MSLT; commonly used for diagnosis) may be insufficiently sensitive and lack adequate reproducibility, more complex protocols are used in some European sleep centers to establish LST, including prolonged undisturbed sleep over a 24- to 48-h period with conventional polysomnography [14,21−23]. However, because of lack of insurance coverage, they are unlikely to be practical in most countries. Debate over idiopathic hypersomnia phenotypes may be unresolved until the pathophysiology is identified [8,23]. Additionally, the classification of idiopathic hypersomnia is still a matter of discussion due to lack of biomarkers, uncertain pathophysiology, dissatisfaction with current diagnostic criteria, and probable heterogeneity of the disorder as currently defined [8,10,24,25].

Idiopathic hypersomnia symptoms typically become apparent during adolescence or early adulthood and are often chronic, although severity can fluctuate and spontaneous improvement and remission (in up to one-third of patients) have been reported [8,16,26,27]. Variations in diagnostic assessment findings (eg, the MSLT) over time may reflect natural fluctuations in disease course or low test-retest stability in this disease; additionally, the MSLT does not measure sleep inertia, one of the key symptoms of idiopathic hypersomnia, particularly in individuals with LST [23,28,29].

Literature reviews on idiopathic hypersomnia [1,9,23,27] and consensus management guidelines [30,31] are available. However, the treatment landscape and clinical research have recently evolved, including the first United States (US) Food and Drug Administration (FDA) approval of an idiopathic hypersomnia treatment (calcium, magnesium, potassium, and sodium oxybates; low-sodium oxybate [LXB]; Xywav® [32,33] and publication of newer randomized controlled trials (RCTs) in idiopathic hypersomnia [11,34]. This paper summarizes clinical data relevant to idiopathic hypersomnia treatment, focusing on recent data not incorporated into prior guidelines. It also highlights ongoing challenges in understanding and treating idiopathic hypersomnia and offers expert opinion on management.

2. Pathophysiology of idiopathic hypersomnia

The pathophysiology of idiopathic hypersomnia remains unclear [23]. Proposed contributors include circadian mechanisms (longer circadian period or long biological night) [14,35,36] and an endogenous hypnotic factor that activates gamma-aminobutyric acid type A ($GABA_A$) receptors [37]; however, the latter has not been reproduced [38]. Preclinical models suggest roles for norepinephrine and dopamine [39,40], but not histamine or hypocretin [41,42], in regulating sleep duration. Cerebrospinal fluid (CSF) levels of histamine, monoaminergic transmitters, or metabolites were similar among individuals with narcolepsy, with idiopathic hypersomnia, and without objective sleepiness, although norepinephrine levels in one study correlated with daytime sleepiness [43,44]; however, findings related to CSF histamine levels in idiopathic hypersomnia remain controversial [45]. Differences in pathophysiology may exist between idiopathic hypersomnia with and without LST. Extended polysomnography protocols could help to differentiate people with confirmed idiopathic hypersomnia from controls or people with other hypersomnolence disorders [21,46].

Sleep architecture in people with idiopathic hypersomnia is generally normal, with expected normal non−rapid eye movement (NREM) and rapid eye movement (REM) patterns and normal REM latency [8,14], but one meta-analysis found alterations in some sleep parameters, including decreased sleep onset latency, increased REM sleep percentage, and decreased slow-wave sleep percentage [47]. These latter results are likely due to differing diagnostic criteria between studies. In clinical practice, a subset of patients are noted to have fragmented but long sleep. Clinically assessed comorbid arousal disorders (including sleepwalking, sleep terrors, and sleep-related eating disorders) are not common in idiopathic hypersomnia [48].

3. Tools to assess idiopathic hypersomnia symptoms

Until recently, there were no validated instruments to assess the complete symptom profile of idiopathic hypersomnia vs other sleep disorders. Most clinical studies measured EDS or overall efficacy (eg, with a visual analog scale [49]) using tools developed for other conditions, such as narcolepsy or obstructive sleep apnea (OSA). Such tools include the Epworth sleepiness scale (ESS [50]) and

maintenance of wakefulness test (MWT [51]). Other idiopathic hypersomnia symptoms (sleep inertia, prolonged nighttime sleep, cognitive impairment, functional consequences) are seldom evaluated in clinical studies, largely due to a lack of validated instruments in this population. A sleep inertia questionnaire (SIQ), validated only in depression, is a self-report measure to assess physiological, cognitive, emotional, and behavioral correlates of the sleep-wake state, and was used in a clustering analysis of hypersomnolence disorders [52,53]. Two unvalidated scales have been used in clinical studies to assess sleep inertia; in one, treatment effects on sleep inertia were rated by patients and neurologists on a scale ranging from 0 (complete lack of benefit) to 3 (major benefit) [54], and in the other (mean visual analog scale for sleep inertia [VAS-SI]), participants self-reported difficulty awakening each morning on a scale ranging from 0 (very easy) to 100 (very difficult) [11]. The psychomotor vigilance task (PVT), a simple, 5- or 10-min assessment requiring a quick response (button press) to a visual stimulus, is an interesting tool for objectively studying sleep inertia that has been used in 2 treatment studies, with reaction time and lapses as measures [37,55,56]. The hypersomnia severity index (HSI), a patient-centered outcome measure to assess hypersomnia symptoms and associated distress and impairment, was validated in a mixed population of patients with central disorders of hypersomnolence, including narcolepsy, idiopathic hypersomnia, and hypersomnia associated with a psychiatric disorder [57,58].

The idiopathic hypersomnia severity scale (IHSS) is a self-report instrument to assess the clinical severity of idiopathic hypersomnia, including prolonged nighttime sleep and sleep inertia (frequency, duration, intensity [ie, sleep drunkenness]) [19,59]. The IHSS comprises 14 items that assess key symptoms of idiopathic hypersomnia: nighttime sleep symptoms and related sleep inertia (five items), daytime sleep symptoms and related sleep inertia (four items), and impaired daytime functioning due to hypersomnolence (five items). Individual items are scored from 0 to 3 or 4, with a composite score ranging from 0 to 50 (higher scores reflecting more severe or frequent symptoms). The mean total IHSS score of healthy controls is 10, and an IHSS total score of 22 is the best cutoff value for discriminating between untreated patients with idiopathic hypersomnia and healthy controls [19]. Disease severity categories are defined in terms of total IHSS score, as follows: mild, 0–12; moderate, 13–25; severe, 26–38; very severe, 39–50 [59]. The estimated minimally clinically important difference between untreated and treated people with idiopathic hypersomnia is 4 points [59]. The IHSS has several advantages: it was validated in idiopathic hypersomnia specifically, in large populations (N = 102 [19] and N = 226 [59]) of treated and untreated patients; it demonstrated specificity and reliability in detecting clinically significant changes following treatment [19,59]; and it was employed in an RCT of LXB in idiopathic hypersomnia [11]. In a validation study, people with idiopathic hypersomnia with LST (>9 h, determined by IHSS item 1) had a higher IHSS total score (indicating more severe symptoms) and total score even after exclusion of item 1, compared with people with idiopathic hypersomnia without LST (≤9 h), and they were also more likely to report severe or very severe symptoms [59]. In the RCT of LXB, treatment effects were demonstrated using the IHSS in both people with LST and people without LST, suggesting that the IHSS, similar to the ESS, performs adequately in assessing symptom severity in both subgroups [11].

4. Nonpharmacologic management

Planned, preventive naps are often unrefreshing in idiopathic hypersomnia with LST, unlike narcolepsy [1,14,15,30], as patients often experience sleep inertia following naps, without immediate restoration of alertness [1]. Patient education to increase awareness of symptoms and management is important. Avoiding even minor sleep deprivation, maintaining a light/dark cycle, regular nocturnal sleep scheduling, and overall self-care can be encouraged, despite no scientific evidence of benefit [60]. In one survey, 96% of respondents with self-reported idiopathic hypersomnia (n = 129) were using nonpharmacologic strategies, including caffeine (82%), daytime naps (81%), scheduled night sleep (75%), exercise (58%), temperature manipulation (47%), and diet (40%) [61]. Notably, during the COVID-19 pandemic, many patients with idiopathic hypersomnia were forced to work from home, an experience that was generally well received. Indeed, 88 survey respondents with idiopathic hypersomnia reported a freer napping schedule, circadian realignment (62% went to bed later, 80% woke up later), decreased commuting time, increased nighttime sleep (from 8.3 to 9.6 h on average), a small decrease in sleepiness, reduced fatigue, improved concentration, increased quality time, and improved well-being [62]. Thus, more frequent teleworking days and scheduling accommodations may benefit patients with idiopathic hypersomnia [63].

5. Pharmacologic treatment

Until 2021, when LXB was approved by the US FDA for the treatment of adults with idiopathic hypersomnia [32], pharmacologic treatment consisted primarily of off-label use of wake-promoting agents [23,27]. Off-label medications exhibited suboptimal symptom control in 39% to 64% of patients with idiopathic hypersomnia, often necessitating use of high-dose medication and/or combination therapy [16,64].

Clinical data in idiopathic hypersomnia expanded slowly after publication of the first small study of modafinil (Provigil®) in 1988 [65], but accelerated beginning in 2009. Through 2018, almost all studies were observational, with only three RCTs that included idiopathic hypersomnia cohorts (10–33 participants; Table S1). Between 2018 and 2022, seven additional idiopathic hypersomnia studies were published, including two modafinil RCTs [34,66], one modafinil retrospective study [67], one SXB retrospective study [68], one LXB RCT [11], a large questionnaire-based registry study [64], and a study of cognitive behavioral therapy for hypersomnia (CBT-H) [69] (Table S2). Although the quality and comparability of studies are complicated by non-standardized definitions of idiopathic hypersomnia and differences in endpoints [27], these are encouraging trends toward generation of much-needed, higher-quality research in this field.

As with any disease, emergence of data can outpace evolution of guidelines. In the most recent French guidelines (Table S3) [30] and American Academy of Sleep Medicine (AASM) guidelines (Table S4) [31], only modafinil was categorized as a first-line option or given a strong recommendation. Other drugs with lesser recommendations include methylphenidate and amphetamines, clarithromycin, flumazenil, mazindol, pitolisant (Wakix®), and sodium oxybate (SXB; Xyrem®). Clinical study data, focusing particularly on recent RCTs, are reviewed below and summarized in Tables S1 and S2.

5.1. Oxybates

5.1.1. Low-sodium oxybate

LXB has a unique composition of cations (calcium, magnesium, potassium, sodium) resulting in 92% less sodium than SXB (a reduction of 1013–1509 mg at the recommended dosage range of 6–9 g/night) [70,71]. In the US, LXB is approved for the treatment of idiopathic hypersomnia in adults and for cataplexy or EDS in patients 7 years and older with narcolepsy [32]. In narcolepsy, the safety profiles of LXB and SXB appear similar [32,72]. LXB is not included in the French [30] and AASM guidelines [31], which were

developed before the 2021 and 2022 publications of the LXB study results.

Support for LXB efficacy in idiopathic hypersomnia is based on a phase 3, multicenter, placebo-controlled, double-blind, randomized withdrawal clinical trial (N = 154), which evaluated the effect of LXB on symptoms including EDS, sleep inertia, functioning, and quality of life, and was the first clinical study to include a validated tool for the assessment of treatment-related changes in idiopathic hypersomnia symptoms (the IHSS) [11]. Participants were adults with idiopathic hypersomnia per ICSD-2 [73] or ICSD-3 [8] criteria and average nocturnal total sleep time ≥7 h, with or without LST, and either taking medications for the treatment of idiopathic hypersomnia or treatment naive. The participants entered a 10- to 14-week open-label titration and optimization period, then a 2-week, open-label, stable-dose period (SDP). At the end of the SDP, eligible participants were randomized 1:1 to 2 weeks of double-blind treatment with placebo or continued LXB. Following the double-blind randomized withdrawal period (DBRWP), participants completed 24 additional weeks of open-label LXB treatment. The primary efficacy endpoint was change in ESS score from the end of the SDP to the end of the DBRWP. Key secondary endpoints were change in IHSS total score from the end of the SDP to the end of the DBRWP, and the proportion of participants reporting worsening of symptoms on the patient global impression of change (PGIc) at the end of the DBRWP relative to the end of the SDP. Change in daytime functioning (assessed using the functional outcomes of sleep questionnaire, short version [FOSQ-10]) from the end of the SDP to the end of the DBRWP was another secondary endpoint. Exploratory endpoints included change in sleep inertia (assessed using the VAS-SI), and change in work and activity impairment (assessed using the work productivity and activity impairment questionnaire: specific health problem [WPAI:SHP]), from the end of the SDP to the end of the DBRWP.

ESS and IHSS scores decreased (indicating improvement) with open-label LXB treatment from baseline to the end of the SDP [74]. During the DBRWP, participants randomized to placebo experienced worsening in mean ESS and IHSS scores and PGIc ratings, whereas participants randomized to LXB maintained improvements from baseline [11]. Better outcomes were also observed with LXB vs placebo for sleep inertia (VAS-SI), daytime functioning (FOSQ-10), and work and activity impairment (WPAI:SHP). Post hoc analyses demonstrated that the improvement in ESS scores with LXB treatment was similar in subgroups defined by idiopathic hypersomnia phenotype (with or without LST), sex, dosing regimen (once or twice nightly), and baseline idiopathic hypersomnia treatment (taking medication or treatment naive).

In the safety population, the most frequent treatment-emergent adverse events (TEAEs) were nausea (22%), headache (18%), dizziness (12%), anxiety (11%), and vomiting (11%) through the end of the 24-week open-label treatment period; 26 participants (17%) discontinued due to TEAEs during LXB treatment [11].

This study represents a significant advance in a therapeutic area with few treatment options and scant robust evidence, as this is the first registrational trial to support FDA approval for the treatment of adults with idiopathic hypersomnia. Besides the sizable cohort, other notable aspects of the study include multiple endpoints to assess symptoms and consequences of idiopathic hypersomnia beyond EDS. The open-label titration phase allowed for dropout of participants who were unresponsive to or intolerant of LXB, increasing the likelihood that the remaining participants would complete the double-blind portion for a comparative efficacy analysis vs placebo. This type of trial closely resembles how this drug is prescribed in real-world clinical practice, in which the first step is to assess tolerability through slow dosage increase. Thirty-eight participants discontinued before the double-blind treatment period for these or other reasons. For the majority of participants responding to and tolerating LXB, study evidence strongly supports significant benefits in idiopathic hypersomnia.

5.1.2. Sodium oxybate

SXB, the sodium salt of gamma-hydroxybutyrate, is a central nervous system depressant approved in the US for the treatment of cataplexy or EDS in patients ≥7 years of age with narcolepsy [72] and in Europe for the treatment of narcolepsy with cataplexy in adult patients, adolescents, and children ≥7 years of age [75]. SXB is not approved for the treatment of idiopathic hypersomnia. SXB is noted in 2017 French guidelines to be potentially effective for the treatment of EDS and sleep inertia in idiopathic hypersomnia [17] and is conditionally recommended for the treatment of idiopathic hypersomnia in 2021 AASM guidelines [18].

Two published studies evaluated SXB in idiopathic hypersomnia [54,68]. The first was a retrospective chart review of open-label administration in 46 adults with idiopathic hypersomnia insufficiently managed with stimulants [54]. SXB was used together with one or more stimulant drugs in 76% of patients. Mean (SD) time on SXB therapy was 15.8 (18.6) months. SXB-based therapy was associated with an ESS reduction of 3.5 points. Other improvements included benefits in sleep inertia (71%), EDS (55%), and shortened nighttime sleep duration (52%) [54]. These outcomes were similar to those in 47 patients with narcolepsy type 1, despite the narcolepsy cohort using significantly higher maximum SXB doses than the idiopathic hypersomnia cohort (mean [SD], 6.6 [2.8] vs 4.3 [2.2] g/night, respectively). This was the first study to document improvement in sleep inertia, one of the most disabling symptoms of idiopathic hypersomnia. Adverse events (AEs) were reported in 67% of patients with idiopathic hypersomnia, primarily nausea (40%) and dizziness (34%).

In a retrospective, real-world, observational study in adults with idiopathic hypersomnia (n = 39), narcolepsy type 1 (n = 26), or narcolepsy type 2 (n = 27) [68], significant improvements from baseline to follow-up 6–24 months later were noted with SXB on the ESS, fatigue severity scale, patient health questionnaire, and total sleep time in the overall study population. Change in ESS was significantly greater with SXB based on univariate analysis, although not after multivariate adjustments.

5.2. Modafinil

Modafinil is approved in the US to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder [76] and is approved in Europe in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy [76]. Modafinil was licensed for the treatment of idiopathic hypersomnia in Europe in 1986, but approval was rescinded in 2011 after reevaluation found insufficient evidence to support the indication and reports of rare severe skin reactions [27,77]. Nevertheless, modafinil is the first-line treatment option recommended in 2017 French hypersomnia treatment guidelines [30] and the only strongly recommended treatment in 2021 AASM guidelines for idiopathic hypersomnia [31]. Most data on modafinil in idiopathic hypersomnia are from observational studies [7,16,49,65,67] or small RCTs [66,78,79].

The largest modafinil RCT in idiopathic hypersomnia (N = 71 randomized; 1 withdrew) [34] included participants 16–64 years of age with idiopathic hypersomnia with or without LST (ICSD-2 criteria), Japanese ESS score ≥11, total sleep time ≥6 h on nocturnal polysomnography, average sleep latency <8 min, and ≤1 sleep onset REM period (SOREMP) on the MSLT. Participants who took modafinil for 3 weeks demonstrated improvement in idiopathic hypersomnia symptoms, including significantly increased sleep

latency on the MWT (primary endpoint), decreased Japanese ESS scores, and decreased daytime naps compared with placebo. A significantly higher percentage of participants rated their condition as "very much improved" or "much improved" on the clinical global impression of change scale with modafinil than placebo. The most frequently reported AEs with modafinil were headache (17.6%), dry mouth (8.8%), and nausea (8.8%). In a smaller RCT, participants (n = 31) were adults with idiopathic hypersomnia without LST per ICSD-2 criteria, disease duration >2 years with onset between 10 and 30 years of age, Beck depression inventory <16 points, and CSF hypocretin-1 >110 pg/mL (if available) [79]. Treatment with modafinil for 3 weeks significantly decreased mean ESS score, significantly improved clinical global impression of severity, and numerically (but not significantly) increased mean sleep latency on the MWT compared with placebo. AEs that occurred significantly more frequently with modafinil compared with placebo included headache and gastrointestinal complaints. Meta-analysis of these two RCTs determined that 3 weeks of modafinil treatment significantly reduced ESS scores but not nap frequency compared with placebo [80].

In a prospective observational study [65], mean number of daily sleep episodes (naps), reported using sleep diaries, was reduced significantly from 1.28 to 0.25 after 2 months of modafinil treatment in 15 participants with idiopathic hypersomnia. Most patients (92%) reported no AEs. In a retrospective chart review study, 24/39 (62%) patients with idiopathic hypersomnia taking modafinil monotherapy had an ESS score decrease of >4 points, with decreased daytime napping [16]. Few safety concerns were noted. In a retrospective chart review study that included 85 patients with idiopathic hypersomnia and median follow-up of 2.4 years, 50 patients took modafinil at any time and 25 remained on modafinil monotherapy at the last follow-up visit; 22/50 (44%) reported complete or partial treatment response (assessed qualitatively) and 3/50 (6%) reported a poor response [7]. "Limiting side effects" (ie, issues that limited the ability to increase doses or required discontinuation) of modafinil were primarily related to cost or headache. In a clinical observational study, ESS scores declined with modafinil treatment in participants with idiopathic hypersomnia (n = 104; with LST, n = 60; without LST, n = 44) and narcolepsy (n = 126) [49]. Mean change in ESS score was significantly greater in participants with idiopathic hypersomnia without LST compared with idiopathic hypersomnia with LST. AEs were similar in participants with idiopathic hypersomnia compared with narcolepsy, and included nervousness, palpitations, and headache.

Two small crossover RCTs evaluated driving performance in individuals with idiopathic hypersomnia or narcolepsy after 5 days of modafinil treatment or placebo [66,78]. Both studies demonstrated improved driving performance with modafinil compared with placebo (fewer inappropriate lane crossings; lower standard deviation of lateral position). An effect on the idiopathic hypersomnia subgroup was not described.

In clinical trials of modafinil (not in idiopathic hypersomnia), the most common AEs with modafinil treatment included headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia; 8% of patients discontinued treatment because of AEs [76].

5.3. Methylphenidate and amphetamines

Treatment with stimulants (methylphenidate, amphetamines, pemoline, mazindol) is common in idiopathic hypersomnia, although clinical data in general, and high-quality data specifically, are scant. Data from the Hypersomnia Foundation's online registry between 2016 and 2018 demonstrated that 51% of individuals with idiopathic hypersomnia were taking at least one of these stimulants [64]. Methylphenidate is recommended as a second-line medication or conditionally in idiopathic hypersomnia guidelines [23,30,31,81] based on one retrospective, observational study [7]. French (but not AASM) guidelines include dextroamphetamine and mazindol as last-line treatment in resistant cases [30,31].

A retrospective chart review study [7] categorized response to therapy in 85 individuals with idiopathic hypersomnia. Among 40 patients who were taking methylphenidate monotherapy at their last follow-up visit, 63%, 33%, and 5% were judged as having a complete, partial, or poor treatment response, respectively, based primarily on qualitative assessment of chart notations regarding symptoms and treatment regimen changes during follow-up visits [7]. Another 21 patients had used methylphenidate at any time during the study. Small numbers of patients were using amphetamine/dextroamphetamine (n = 4), methamphetamine (n = 3), or dextroamphetamine (n = 2) at the most recent follow-up visit; all were assessed as having a complete or partial response to therapy, except for the two treated with dextroamphetamine, who were classified as having a poor response. All three patients who took pemoline were classified as having a complete response. Another retrospective chart review study reported an ESS score decrease of >4 points ("responders") in five of eight (63%) patients with idiopathic hypersomnia taking dexamphetamine monotherapy, and one of three (33%) patients taking dexamphetamine plus modafinil [16]. In a third retrospective chart review study that included 37 patients with idiopathic hypersomnia, mazindol monotherapy or add-on therapy was associated with a significant decrease in ESS scores (mean change, −4.8; mean time on mazindol, 18.3 months) [82]. Mazindol therapy was discontinued in 19 (51%) patients with idiopathic hypersomnia because of lack of efficacy, adverse effects, or other reasons.

5.4. Clarithromycin

Clarithromycin is an antibiotic and negative allosteric modulator of $GABA_A$ receptors [37] that was studied in idiopathic hypersomnia in one small RCT [37] and one observational study [83]. AASM idiopathic hypersomnia guidelines include clarithromycin with a conditional recommendation [31], whereas French guidelines state that it is not indicated [30]. In a double-blind, placebo-controlled, crossover RCT in participants with idiopathic hypersomnia with LST (n = 5), idiopathic hypersomnia without LST (n = 5), and other forms of hypersomnolence (n = 10), 2 weeks of clarithromycin treatment was associated with significantly decreased ESS scores, increased (improved) scores on the FOSQ-10, improved 36-item short form health survey subscale scores, and decreased (improved) Stanford sleepiness scale scores, compared with placebo [37]. However, median reaction time on the PVT, the primary outcome measure, was not significantly different between clarithromycin and placebo. In a retrospective chart review study involving patients with primary hypersomnia (n = 41) or narcolepsy without cataplexy (n = 12), 64% of patients reported improvement in subjective sleepiness with clarithromycin treatment [83].

5.5. Flumazenil

Flumazenil, which is generally believed to antagonize the sedative-hypnotic actions of benzodiazepines at the classical benzodiazepine-binding domain of $GABA_A$ receptors, may reverse enhancement of $GABA_A$ signaling by CSF in people with hypersomnolence in vitro [84]. In a study in seven people with hypersomnolence, intravenous flumazenil normalized psychomotor vigilance and subjective alertness; however, the clinical intervention was preliminary, single blinded, and with a fixed-order

sequence [84]. One study of flumazenil for the treatment of idiopathic hypersomnia has been published [85]. In this retrospective chart review, 36 individuals with treatment-refractory idiopathic hypersomnia were treated with compounded flumazenil formulations (sublingual lozenges, topical cream, or both); 63% of patients had a response, determined using clinical and pharmacy refill records, and electronic correspondence from patients [85]. However, flumazenil is not recommended in French [30] or AASM [31] idiopathic hypersomnia guidelines.

5.6. Pitolisant

Pitolisant is a histamine-3 receptor antagonist/inverse agonist that is approved in the US for the treatment of EDS or cataplexy in adult patients with narcolepsy and in Europe in adults for the treatment of narcolepsy with or without cataplexy [86,87]. Pitolisant is not approved for the treatment of idiopathic hypersomnia. Pitolisant is included in AASM idiopathic hypersomnia guidelines [31] with a conditional recommendation and in French guidelines [30] as an option to be considered when idiopathic hypersomnia is resistant to modafinil and methylphenidate.

In a retrospective chart review study that included 65 patients with idiopathic hypersomnia resistant to other wake-promoting agents, pitolisant as monotherapy or add-on treatment was associated with a small decrease in ESS scores (median change, −1.5; median time on pitolisant, 6 months) [88]. Although 36% of pitolisant users were responders (reduction in ESS $\geq$3), therapy was discontinued in 63%, primarily because of lack of efficacy, AEs, or both [88].

5.7. Melatonin and antidepressants

Although evidence is mixed and it is not recommended in guidelines, melatonin has been taken at bedtime to reduce sleep inertia upon awakening [30,31,89]. Alerting antidepressants have been used to treat idiopathic hypersomnia, but are not included in guidelines [80,89].

6. Discussion and expert opinion

Treatment goals for idiopathic hypersomnia include normalization of functioning (eg, reduction of excessive sleepiness in idiopathic hypersomnia with and without LST; decreased quantity of sleep in idiopathic hypersomnia with LST; increased ability to wake up normally, be on time, and drive safely; and improvement of attention and cognition). As there is currently only one approved treatment for idiopathic hypersomnia, there is as yet no treatment algorithm, and little basis on which to derive standardized protocols. Treatment is necessarily very individualized, taking into account all available options and the patient's unique circumstances.

Management of idiopathic hypersomnia should incorporate pharmacologic and nonpharmacologic strategies. Nonpharmacologic strategies can include educational programs to increase knowledge of idiopathic hypersomnolence symptoms, severity, course, and consequences; scheduled short naps (if refreshing); good sleep hygiene; CBT-H; work and school accommodations; avoiding excessive darkness (eg, use of light therapy to counter negative effects of seasonal changes in light); and purposeful strategies for awakening in the morning (alarms, assistance of others) and for gaining alertness after awakening (ie, aiding in overcoming sleep inertia; measures include light exposure [including use of a light box for 30 min soon after natural awakening], maintaining a strong photoperiod, caffeine, showering, and exercise). For individuals with prolonged nighttime sleep, avoiding sleep deprivation is important. Despite lack of strong evidence for the effectiveness of such measures in idiopathic hypersomnia, they may have some benefits and are devoid of side effects. Comorbidities that may contribute to or result from idiopathic hypersomnia (eg, depression, including in those who sleep longer during dark winter months) should be identified and addressed. Idiopathic hypersomnia is amenable to telemedicine, which may facilitate convenient and regular follow-up.

The relative places of LXB, modafinil, and other medicines in future treatment paradigms are not firmly established, but recommendations may be made based on availability, efficacy and safety data, and clinical experience. For example, LXB is approved for the treatment of idiopathic hypersomnia in the US but is not available outside of the US, whereas SXB is available in the EU, where it is approved only for the treatment of narcolepsy. LXB is generally preferable to SXB due to its substantially lower sodium content, but SXB may be preferable in patients with comorbid hypotension, autonomic instability, or other conditions where increased salt intake is recommended. Additionally, clinicians have significant experience with modafinil in idiopathic hypersomnia, and a good sense of its safety profile in this disorder. Modafinil and amphetamines may be more helpful in people with idiopathic hypersomnia without long sleep compared with long sleepers, although short-acting amphetamine may be helpful once awake. Having multiple effective therapies in a clinician's armamentarium will better enable individualization of therapy. Because idiopathic hypersomnia is a heterogeneous disorder with symptoms that vary in severity among patients and from time to time, the therapeutic profile of particular medicine(s) may be matched to clinical presentation (including presence or absence of LST and severe sleep inertia), comorbidities, lifestyle and other circumstances, and adverse effects, as outlined in the following examples.

6.1. Individualized pharmacotherapy

To identify an appropriate pharmacologic treatment, it is important to be confident in the diagnosis of idiopathic hypersomnia (as opposed to other sleep disorders) and phenotype (with or without LST; duration/severity of LST), and consider the patient's particular constellation of symptoms, lifestyle, and other circumstances. Focusing on the individual patient's key symptom(s) may be advisable as a first step. Patients with normal sleep durations are less likely to have severe sleep inertia [15] and more likely to respond to both oxybate and non-oxybate therapies, whereas people with severe sleep inertia and LST may benefit the most from oxybate, as LXB may best treat these symptoms [11].

As LXB is a relatively new treatment option, the approach to optimization of dosing and regimen is not standardized; for example, it remains unclear whether once-nightly or twice-nightly dosing is preferable based on the presence of LST, although the regimen can be adjusted based on the success of the initial approach. In patients without LST, a titration process similar to that used in narcolepsy may be effective, including a low starting dosage (eg, 3.0–4.5 g/night) with gradual increase as needed. Some clinicians prefer to begin with twice-nightly dosing and others prefer to begin with once-nightly dosing. Patients with great difficulty awakening during the night for the second dose may find that a single dose at bedtime is sufficient; alternatively, once-nightly dosing may trigger awakening in the middle of the night (ie, end-of-dose effect), allowing (after a few weeks) for a second dose to be taken for greater efficacy. A shift to asymmetric dosing (with the first nightly dose being higher than the second) may be effective in some cases. In patients with LST, the titration process may be more complex, and can take weeks or months to optimize. Patients with very long sleep time may find it easier to wake up in the morning

but then feel more sleepy during the day, or may experience a temporary circadian phase delay that leads to sleep-onset insomnia as their sleep shortens. In patients with extreme LST and sleep inertia, a combination of delayed dosing, melatonin in the evening, and bright light in the morning may be helpful. Patients with LST that is fragmented may improve to having more consolidated sleep with LXB treatment, and may benefit from thrice-nightly dosing to maintain oxybate levels throughout the night. For all patients, further dose and regimen adjustments may be needed to minimize gastrointestinal issues and mood changes. Overall, flexibility is important. It is important to counsel patients that it might take weeks or months to achieve maximal benefit with LXB.

Drug combinations may also offer possibilities for timing of administration (eg, LXB at bedtime, stimulants at awakening) to maximize effectiveness. However, polytherapy and monotherapy must be compared to ascertain incremental benefit. Patients complaining of residual attention deficit when treated with LXB or modafinil may be switched to, or treated concomitantly with, off-label medications such as pitolisant or methylphenidate. Pitolisant and other histamine modulators, as well as orexin agonists (if approved), are likely to benefit patients, but response heterogeneity should be expected given the spectrum of symptoms and sleep duration in idiopathic hypersomnia; formal study and clinical trials are needed.

6.2. Comorbidities

Caution should be used when treating patients who have idiopathic hypersomnia and depressive symptoms, as several medications (eg, modafinil, pitolisant, SXB, LXB, methylphenidate, and amphetamines) may exacerbate (or, in rare instances, trigger) depression [90]. Obesity may favor the use of LXB in the absence of OSA, as decreases in weight and/or body mass index have been observed with oxybate treatment in people with narcolepsy [32,72,75,91–95] and idiopathic hypersomnia [96]. In patients with a history of cardiovascular disease, stimulants should be used with caution [30]. SXB has a warning regarding high sodium for patients with heart failure, hypertension, renal impairment, or other conditions that are sensitive to sodium; LXB does not have this warning and may be appropriate for people with cardiovascular concerns [32,72,75].

6.3. Side effects and other safety considerations

LXB is an efficient long-term drug for idiopathic hypersomnia, in the authors' clinical experience, but patients must tolerate it, and side effects are initially more frequent than with modafinil. This places modafinil as first-line treatment for many patients. Alternatively, a slow increase in LXB dosing may help with tolerability. SXB may be an alternative option when LXB is unavailable due to insurance coverage or other issues. Enuresis and/or sleepwalking, which were associated with oxybate treatment in clinical trials, may discourage use of oxybate if they occur and are persistent; however, enuresis may be less of a concern with LXB than SXB, and is more common in pediatric patients than adults. Abuse and misuse of gamma-hydroxybutyrate, the active moiety of LXB, is associated with central nervous system adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death [32]; hence, LXB may not be ideal for people with a history of substance abuse, hospitalization for depression, or suicide attempts.

Patients with idiopathic hypersomnia are often women (66%–75%), some of child-bearing potential. Modafinil reduces the effectiveness of not only oral contraceptives, but also vaginal rings and transdermal forms of estrogens and progestin; hence, other options may be preferred by women taking those medications [76,97]. Intrauterine devices remain effective when combined with modafinil. However, modafinil may interfere with the anti-bleeding effect of progestin, whether as a coating in an intrauterine device or when taken with estrogen by postmenopausal women. On the other hand, parents who need to awaken at night to care for their babies may prefer modafinil over LXB due to concerns about hypo-arousability with oxybate.

7. Conclusion

Clinicians should feel empowered by new knowledge and disease-specific assessments to make optimal choices for their patients with idiopathic hypersomnia. The addition of LXB to the treatment armamentarium of idiopathic hypersomnia is an important development, although other medications will retain a place in therapy, to be better defined after more experience with LXB. However, further progress is needed, particularly regarding uniformity in defining treatment success in idiopathic hypersomnia. Furthermore, development of a validated assessment tool specific to idiopathic hypersomnia (ie, the IHSS) should aid future clinical research and may be useful in clinical practice to monitor patient progress.

8. Practice points

1. Treatment of idiopathic hypersomnia with off-label wake-promoting or stimulant medications may have limited success, especially for sleep inertia and prolonged nighttime sleep.
2. Modafinil is not approved for the treatment of idiopathic hypersomnia, but has been tested in randomized placebo-controlled studies in idiopathic hypersomnia and used for decades.
3. The recent approval of low-sodium oxybate in the Unites States to treat adults with idiopathic hypersomnia represents a significant shift in the treatment paradigm, particularly in light of its clear benefits on all symptoms of idiopathic hypersomnia, including daytime sleepiness, severe sleep inertia, prolonged nighttime sleep, and quality of life.
4. Sleep duration is an important consideration when choosing strategies for therapy and tracking outcome.
5. Clinical consensus and expert opinion remain crucial to guiding management of this debilitating condition.

9. Research agenda

1. Disease awareness should be raised to facilitate accurate diagnosis.
2. Treatment guidelines should be updated at the next opportunity to include the latest data and to include medications for idiopathic hypersomnia that are approved at that time.
3. Rigorous clinical studies are needed for many of the alerting agents and other medications being used off-label.
4. Better practical understanding of when and how to use low-sodium oxybate is needed.
5. Disease phenotypes need to be clarified and studied for possible relevance to treatment choices.
6. A treatment algorithm should be developed to assist clinicians with development of personalized treatment plans, taking into account disease severity (eg, excessive daytime sleepiness, long sleep time, sleep inertia), age, comorbidities (eg, depressive symptoms, cardiovascular problems), and concomitant medications.

7. It is important to use validated scales such as the idiopathic hypersomnia severity scale in clinical research and possibly in clinical practice; additional validated, specific instruments would be welcome.
8. Wearable devices will likely be a way forward for tracking responses to treatment; high-quality consumer types, coupled with smartphone-based symptom capture, may allow for optimal titration of therapy beyond episodic clinical visits.

Declaration of competing interest

Isabelle Arnulf has participated in advisory boards for UCB Pharma, Idorsia (2020), Ono Pharma (2019), and Roche Pharma (2019).

Robert Thomas has patents and licenses for ECG-spectrogram, licensed to MyCardio, LLC through the Beth Israel Deaconess Medical Center, and for auto-CPAP algorithm, licensed by BIDMC to DeVilbiss-Drive; holds an unlicensed patent for a CO_2 device for central/complex sleep apnea; is a general sleep medicine consultant for GLG Councils and Guidepoint Global; and is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals.

Asim Roy has received consultancy fees from Jazz Pharmaceuticals and Harmony Biosciences.

Yves Dauvilliers is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Avadel, Idorsia, Takeda, Harmony Biosciences, and Bioprojet.

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Appendix A. Supplementary data

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