Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2025-122

Case Report

Open Access

Idiopathic Hypersomnia: Clinical Insights and Advances in Diagnosis and Management

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Received: November 05, 2025
Accepted: December 04, 2025
Published: December 08, 2025

Citation: Luo JJ. 2025. Idiopathic Hypersomnia: Clinical Insights and Advances in Diagnosis and Management. *J Neurol Exp Neurosci* 11(2): 08-14.

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Published by United Scientific Group

Abstract

Idiopathic hypersomnia (IH) is a chronic central hypersomnolence disorder that impairs daily functioning and quality of life. Lacking definitive biomarkers, IH is frequently misdiagnosed or mistaken for psychiatric conditions. Diagnostic challenges include the limited specificity of the multiple sleep latency test (MSLT) in distinguishing IH from narcolepsy type 2 (NT2). Accurate diagnosis requires exclusion of other causes and objective evaluation with actigraphy or extended polysomnography (PSG). Evidence of GABAergic dysfunction suggests potential biomarkers. Low-sodium oxybate improves sleepiness and inertia. This review summarizes current knowledge of IH pathophysiology, highlights key diagnostic considerations, and provides an evidence-based overview of therapeutic approaches and future research directions aimed at improving individualized care.

Keywords: Central disorder of hypersomnolence, Excessive daytime sleepiness, Idiopathic hypersomnia, Narcolepsy

Introduction

Sleep is a fundamental physiological process essential for human health, supporting metabolic regulation, cognitive performance, emotional stability, immune defense, brain plasticity, and cardiovascular function [1]. While insomnia has long been the focus of clinical attention, central disorders of hypersomnolence, including IH, remain significantly underrecognized leading to substantial delays in diagnosis and treatment [2]. IH is characterized by persistent, disabling excessive daytime sleepiness (EDS) despite adequate or even prolonged nocturnal sleep, frequently resulting in marked impairments in occupational productivity, interpersonal relationships, and quality of life [3].

Accurate differentiation of IH from narcolepsy and other hypersomnia syndromes requires detailed understanding of sleep architecture, neurochemical regulation, and appropriate application and interpretation of objective diagnostic tools such as the MSLT and PSG [4]. Although clinical diagnostic criteria for IH are well-defined in the American Academy of Sleep Medicine International Classification of Sleep Disorders-Third Edition, Text Revision (ICSD-3-TR) [4], treatment options remain limited and frequently provide incomplete symptom control [3]. The discovery of abnormal potentiation of gamma-aminobutyric acid A receptor ($GABA_A$) activity in a subset of IH patients, along with the U.S. Food and Drug Administration (FDA) approval of novel pharmacologic agent, low-sodium oxybate, have begun to reshape our understanding of IH pathophysiology [5, 6]. This review aims to provide clinicians and researchers with an overview of IH, emphasizing its neurophysiological mechanisms, clinical manifestations, differential diagnosis, and evidence-based therapeutic strategies, with the goal of

improving patient care and guiding future research directions.

Sleep Physiology

Sleep is an active, dynamic neurophysiological state governed by homeostatic and circadian processes. The suprachiasmatic nucleus (SCN) of the hypothalamus serves as the master circadian pacemaker, orchestrating hormonal secretion, body temperature, and sleep-wake rhythms through endogenous near 24 h cycles, coordinating physiology and behavior with the external light-dark cycle.

Neurotransmitter systems in sleep-wake regulation

Wakefulness is maintained by a network of ascending arousal systems that originate in the brainstem and hypothalamus and project widely to the cortex and thalamus (Figure 1). Key monoaminergic nuclei include the locus coeruleus (LC), which releases norepinephrine (NE) to enhance cortical excitability and vigilance [7]; the dorsal raphe nuclei, which release serotonin to modulate mood and cortical activation [8]; and the tuberomammillary nucleus (TMN) of the posterior hypothalamus, the sole source of central histamine, which promotes sustained wakefulness [9]. Dopaminergic neurons in the ventral tegmental area and substantia nigra also contribute to arousal, reward, and motivated behaviors that reinforce wake states [10].

Cholinergic neurons in the pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmental nuclei (PPT and LDT), along with basal forebrain cholinergic projections, facilitate cortical activation and electroencephalogram (EEG) desynchrony during both wakefulness and rapid eye movement (REM) sleep, underscoring their complex role in vigilance states [11]. Additionally, orexin (also named hypocretin)-producing neurons in the lateral hypothalamus (LH) provide excitatory input to these monoaminergic and cholinergic systems, stabilizing wakefulness and preventing inappropriate transitions into sleep; loss of orexin signaling is a key pathophysiological feature of narcolepsy [12].

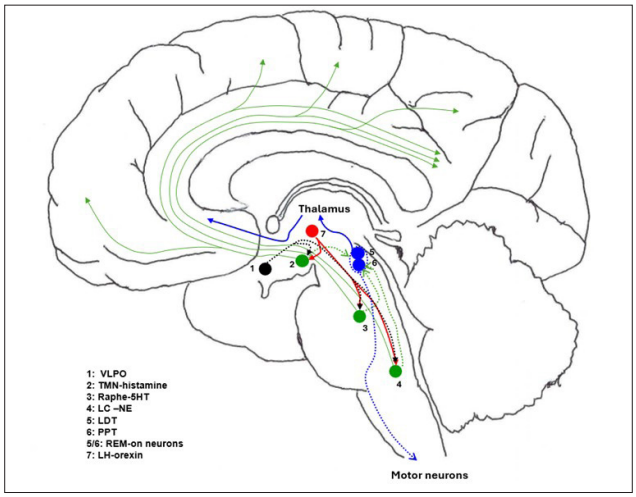


Figure 1: (1) VLPO: Releases GABA to inhibit arousal-promoting nuclei, facilitating sleep onset. **(2)** TMN: The sole source of central histamine, promotes sustained wakefulness. **(3)** Dorsal raphe nuclei: Release serotonin (5-HT) to modulate mood, cortical activation, and arousal. **(4)** LC: Releases NE to enhance cortical excitability and vigilance. **(5)** LDT: Cholinergic projections contribute to cortical activation and EEG desynchrony. **(6)** PPT: Works with LDT to release acetylcholine during wakefulness and REM sleep. 5/6: REM-on neurons: Active during REM sleep, supporting EEG desynchrony and cortical arousal. **(7)** LH: Orexin (hypocretin) neurons provide excitatory drive to monoaminergic systems to stabilize wakefulness.

In contrast, sleep initiation and maintenance rely on inhibitory neurotransmission and homeostatic mediators. GABA-producing neurons in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus exert inhibitory control over arousal-promoting nuclei, effectively "shutting down" wake-promoting systems to allow sleep onset [13]. Adenosine, a byproduct of cellular metabolism, accumulates during wakefulness and acts as a sleep-promoting neuromodulator by inhibiting cholinergic neurons in the basal forebrain and disinhibiting VLPO neurons, thereby integrating homeostatic sleep pressure [14]. Melatonin, synthesized by the pineal gland under circadian control from the SCN, facilitates sleep initiation by promoting circadian phase alignment and lowering core body temperature [15]. Serotonin, while promoting wakefulness in the dorsal raphe, also plays nuanced roles in non–REM (NREM) sleep regulation through complex receptor-mediated actions in different brain regions [16]. These interlocking neurotransmitter systems underscore the dynamic balance between arousal and sleep, with precise regulation essential for healthy sleep-wake cycles and vulnerability to sleep disorders when disrupted (Figure 1).

Sleep architecture and physiological roles

Human sleep is a highly organized neurophysiological process that cycles through distinct stages, broadly categorized into REM sleep and NREM sleep. NREM sleep is further divided into three stages-N1, N2, and N3-each characterized by specific EEG patterns and physiological functions (Table 1).

N1 sleep, or stage 1, represents the initial transition from wakefulness to sleep. It is marked by the appearance of low-amplitude theta waves (4 - 7 Hz) on EEG and typically comprises 5% of total sleep time. This stage serves as transitional gateway into deeper sleep and is associated with reduced environmental awareness and slow rolling eye movements [17].

N2 sleep, or stage 2, is the predominant stage of NREM sleep, accounting for approximately 45 - 55% of total sleep. It is characterized by the presence of sleep spindles (bursts of 12 - 14 Hz activity) and K-complexes on EEG, reflecting thalamocortical gating mechanisms that protect the brain from arousal by external stimuli [18]. N2 plays a key role in procedural learning, autonomic regulation, and cardiovascular stability [19].

N3 sleep, previously subdivided into stages 3 and 4 and often termed slow-wave sleep (SWS), is distinguished by high-amplitude, low-frequency delta waves (0.5 - 3 Hz). N3 represents the deepest stage of NREM sleep and is essential for physical restoration, immune modulation, synaptic homeostasis, and memory consolidation, particularly declarative memory [20-22].

REM sleep is characterized by a desynchronized EEG pattern showing low-voltage, mixed-frequency waves,

Table 1: Physiological features across sleep stages.

Sleep stage	EEG signature	Key physiological functions
N1 (Light sleep)	Low-amplitude, mixed-frequency waves	Transition from wakefulness; reduced muscle tone; slow eye movements
N2 (Intermediate sleep)	Sleep spindles and K-complexes	Memory consolidation; reduction in heart rate and body temperature
N3 (SWS)	High-amplitude, low-frequency delta waves	Tissue repair; immune system support; metabolic regulation; memory consolidation
REM sleep	Low-amplitude, mixed-frequency waves with sawtooth patterns	Dreaming; synaptic plasticity; emotional memory consolidation; muscle atonia except for eye and respiratory muscles

accompanied by REM, muscle atonia, and vivid dreaming. REM sleep typically begins approximately 90 min after sleep onset and recurs cyclically throughout the night, lengthening in duration with each successive cycle [23]. REM sleep is crucial for emotional regulation, neurocognitive integration, and memory consolidation, particularly emotional and procedural memory, through hippocampal-neocortical integration [20].

Sleep consists of 4 - 6 cycles of 90 - 120 min, with SWS dominating early and REM later, influenced by circadian rhythms [22]. Cellular repair accelerates during sleep through macromolecule synthesis and growth hormone release, peaking in SWS [22]. NREM also supports immunity by promoting pro-inflammatory cytokines for defense while balancing anti-inflammatory responses to prevent overactivation [21].

Synaptic homeostasis hypothesis suggests that wakefulness promotes synaptic potentiation through learning, which sleep counterbalances via downscaling to maintain functional strength and conserve energy. NREM sleep, especially SWS, supports this renormalization, preserving cognitive flexibility and learning capacity [24-26]. REM sleep is crucial for consolidating emotionally salient and procedural memories through hippocampal–neocortical communication, which supports long-term information storage [20]; it also contributes to emotional regulation by modulating amygdala reactivity to negative stimuli [24-26].

Sleep deprivation and health

Sleep deprivation disrupts essential physiological functions and produces widespread systemic effects. It impairs immunity, increasing infection risk and diminishing vaccine effectiveness [27]. Sleep loss also impairs glucose metabolism, raises cortisol, activates the sympathetic system, and promotes inflammation, contributing to obesity, diabetes, and cardiovascular disease [28]. Neurocognitively, it reduces attention, memory, and executive function while increasing emotional instability and mood disorder risk [29]. Sleep is thus a foundational pillar of health requiring clinical and public health attention.

Hypersomnia/EDS and health

Hypersomnia and EDS are increasingly recognized as markers of adverse cardiovascular and cerebrovascular health. EDS is associated with higher risks of hypertension, coronary artery disease, heart failure, atrial fibrillation, stroke, and cardiovascular mortality, independent of traditional risk factors and coexisting sleep disorders [30]. These associations suggest that EDS may reflect underlying pathophysiologic vulnerability rather than symptom burden alone. Proposed mechanisms include autonomic dysregulation, chronic systemic inflammation, metabolic dysfunction, and neurohumoral imbalance [30]. Supporting this, real-world evidence indicates that individuals with IH have approximately two-fold higher odds of major adverse cardiovascular events, including myocardial infarction, heart failure, and stroke, compared with matched controls [31].

Useful Tools in Sleep Studies

Subjective tools

The Epworth sleepiness scale (ESS) is the most widely used standardized questionnaire to quantify habitual daytime sleepiness, asking respondents to rate their likelihood of dozing in eight routine situations. Scores ≥10 suggest abnormal sleepiness, ≥18 indicate severe impairment [32]. Although subjective, ESS correlates moderately with objective measures of sleep propensity and is valuable in longitudinal monitoring [33].

Clinical interviews remain essential for eliciting symptom duration, sleep-wake timing, naps, and sleep inertia. Sleep diaries, kept for at least 1 - 2 weeks, help identify chronic long sleep times, irregular schedules, and patterns suggesting insufficient sleep or circadian disorders [34].

Disorder-specific tools, such as the IH severity scale, capture IH related symptoms, including excessive sleep and inertia, improving phenotyping and treatment tracking [35].

Objective tools

Objective testing is central to diagnosing hypersomnolence disorders. PSG evaluates sleep architecture and excludes comorbidities like obstructive sleep apnea (OSA), limb-movement disorder, or parasomnias [36]. For IH, PSG should show >6 h total sleep and >85% efficiency without major sleep-disrupting pathology [4].

The MSLT, performed after PSG, is the gold-standard for pathological sleepiness [37]. IH is diagnosed when mean sleep latency <8 min with ≤1 sleep-onset REM period (SOREMP), while narcolepsy requires ≥2 SOREMPs [38]. Limitations including night-to-night variability, poor reliability, and confounders such as insufficient sleep or medications [39]. Proper interpretation requires preparation with diaries or actigraphy and control of external factors (medication, caffeine, and circadian influences) [3].

Actigraphy, continuous wrist monitoring for 1 - 2 weeks, objectively tracks sleep-wake patterns and complements diaries, confirming adequate sleep and ruling out circadian disorders [40]. Consumer-grade devices with validated algorithms are increasingly used for screening [41].

Biomarkers

Orexin/Hypocretin for narcolepsy type 1 (NT1): In NT1, orexin-producing neurons are lost, which cause cerebrospinal fluid (CSF) orexin-A <110 pg/mL [12] and destabilized sleep-wake transitions, lead to cataplexy and SOREMPs [2]. NT2 and IH typically show normal or intermediate CSF levels (110 - 200 pg/mL) [42], making orexin measurement useful for differentiation [43].

GABAergic potentiation in IH: Some IH patients' CSF enhances $GABA_A$ receptor currents, increasing inhibitory signaling and causing symptoms like sleep inertia and cognitive fog. This suggests a potential biomarker [5] and therapeutic target [44]; and flumazenil has anecdotally been tested to counteract this effect [45].

Neuroimaging and electrophysiology: fMRI and EEG reveal altered thalamocortical activity and increased beta-frequency during NREM in IH, but these remain investigational and not clinically validated [46].

Central Hypersomnolence Disorders

Central hypersomnolence disorders cause EDS not due to insufficient sleep or circadian misalignment (Table 2).

NT1: Defined by EDS with cataplexy and severe orexin loss (CSF orexin-A < 110 pg/mL) [43], leading to unstable sleep-wake transitions, sleep attacks, hallucinations, paralysis, and SOREMPs on MSLT [2]. Notably, human leukocyte antigen (HLA)-DQB1*06:02 is present in more than 85% of NT1 patients but also in 12 - 38% general population [47].

NT2: Presents with EDS but no cataplexy; CSF orexin levels are normal or intermediate (110 - 200 pg/mL) [42]. Diagnosis requires MSLT latency ≤8 min and ≥2 SOREMPs [2]. Some NT2 cases may evolve into NT1 if cataplexy emerges.

IH: Chronic EDS without cataplexy, often with >10 h sleep and severe sleep inertia. MSLT shows latency ≤8 min and <2 SOREMPs [3]. Pathophysiology may involve GABAergic tone [5] or impaired sleep homeostasis [48].

Kleine-levin syndrome (KLS): Rare, episodic hypersomnia lasting day-weeks, with behavioral changes like hyperphagia, hypersexuality, irritability, and confusion [49]. Between episodes, patients are typically asymptomatic. Most common in adolescent males; etiology may involve hypothalamic or autoimmune mechanisms [50].

Secondary hypersomnia: EDS due to identifiable neurologic, psychiatric, or medication-related causes (e.g., Parkinson's, depression, and sedatives). Careful history and targeted tests are essential for differentiation [4].

Diagnostic distinction and approach to IH

Differentiating IH from NT2 is challenging due to overlapping symptoms and imperfect tests. NT2 shows EDS without cataplexy and ≥2 SOREMPs on MSLT with latency ≤8 min, reflecting REM dysregulation [2]. IH, in contrast, presents with EDS, ≤1 SOREMP, and similar short latencies [51]. ICSD-3-TR requires symptoms ≥3 months despite ≥7 h habitual sleep, confirmed by history or actigraphy [4, 51]. IH often involves >11 h nocturnal sleep, severe sleep inertia, and unrefreshing naps [52], unlike NT2 where naps offer temporary relief [53].

MSLT remains central in diagnosis despite limitations [39]. IH shows latency <8 min with ≤1 SOREMP, distinguishing it from NT1/NT2 [51]. Extended PSG can confirm ≥11 h sleep in "long sleeper" with IH [52]. No biomarker reliably separates IH from NT2; orexin levels are normal in both [2]. Exclusion of mimics is essential: rule out OSA via PSG, assess mood disorders, and review medications or neurologic causes.

A structured approach integrating history, objective sleep measures, extended protocols, and systematic exclusion improve diagnostic accuracy and guides treatment.

Therapeutic Approaches

IH management requires a personalized, multimodal plan combining behavioral and pharmacologic strategies.

Non-pharmacologic: Sleep hygiene-consistent schedules, avoiding late stimulants, and limiting screens-supports circadian stability [54]. Morning bright light therapy and structured wake routines help reduce sleep inertia [55].

Table 2: Differential diagnosis of central disorders of hypersomnolence.

Disorder	Key clinical features	Laboratory studies	Neurochemical findings
NT1	EDS, cataplexy, sleep paralysis, hypnagogic/ hypnopompic hallucinations, disrupted nocturnal sleep	MSLT: mean sleep latency ≤8 min with ≥2 SOREMPs; HLA-DQB1*06:02 positive in >85%	Low or undetectable CSF hypocretin-1 (orexin-A)
NT2	EDS without cataplexy; may have sleep fragmentation or hallucinations	MSLT: mean sleep latency ≤8 min with ≥2 SOREMPs; normal/no cataplexy	Normal or intermediate CSF hypocretin-1
IH	EDS without cataplexy, long unrefreshing naps, prolonged nighttime sleep, sleep inertia (sleep drunkenness)	MSLT: mean sleep latency ≤8 min with <2 SOREMPs; often total sleep time >11 h on 24 h PSG	Normal CSF hypocretin-1
KLS	Recurrent episodes of hypersomnia lasting days to weeks, often with hyperphagia, hypersexuality, cognitive or mood disturbances; inter-episode normality	PSG and MSLT are usually normal between episodes; clinical diagnosis based on history	Hypocretin-1 may be normal or mildly reduced during episodes
Secondary hypersomnia (e.g., due to neurologic, psychiatric, pharmacologic causes)	EDS in context of identifiable condition (e.g., TBI, Parkinson's, depression, sedative use); symptoms parallel primary disorder	PSG or MSLT may show variable findings; diagnosis guided by underlying condition	Variable; typically, normal CSF hypocretin unless hypothalamic injury

Table 3: Comparison of medications for IH.

Medication	Mechanism of action	Side effects	Dose (Typical)	Approx. cost (USD)
Low-sodium oxybate (Xywav)	$GABA_B$ agonist; promotes sleep consolidation	Dizziness, nausea, enuresis	4.5 - 9 g/night	$150 - 250/night
Modafinil/Armodafinil	Dopamine reuptake inhibitor; ↑ histamine/orexin	Headache, insomnia, anxiety	100 - 400 mg/day	$10 - 15/day
Methylphenidate/Amphetamines	↑ Dopamine/NE	Tachycardia, insomnia, appetite loss	10 - 60 mg/day	$5 - 10/day
Sodium oxybate (Xyrem)	Same as above (↑ sodium content)	Same as above, ↑ sodium-related risk	4.5 - 9 g/night	$180 - 300/night
Pitolisant (Wakix)	H3 inverse agonist; ↑ histamine release	Headache, insomnia, nausea	17.8 - 35.6 mg/day	$25 - 30/day
Clarithromycin	Negative allosteric modulator of $GABA_A$ receptors; may reduce excessive GABAergic tone	Gastrointestinal issues upset, dysgeusia, QT prolongation, drug-drug interactions	250 - 500 mg/day (usually 250 mg BID)	$5 - 15/day

Brief naps may offer limited benefit; morning exercise can aid alertness [3]. Cognitive behavioral therapy for insomnia may help with comorbid insomnia or maladaptive sleep beliefs [56]. Education, psychological support, and workplace accommodations improve functioning and reduce stigma.

Pharmacologic: Treatment is individualized, considering efficacy, safety, and comorbidities (Table 3).

Low-sodium oxybate (Xywav) is the only medication FDA-approved for IH. A $GABA_B$ receptor agonist, it consolidates nighttime sleep, reduces nocturnal awakenings, and improves EDS and sleep inertia. It is typically dosed at 4.5 - 9 g/night [6]. Side effects include enuresis, dizziness, and nausea [57]. Compared to sodium oxybate (Xyrem), Xywav has reduced sodium content, offering potential cardiovascular benefit in long-term use [6].

Modafinil and armodafinil, non-amphetamine wake-promoting agents that inhibit dopamine reuptake and may enhance histaminergic and orexinergic signaling, are commonly used first-line [58]. They are generally well tolerated, with headache, anxiety, nausea, and insomnia as the most frequent side effects. Doses range from 100 to 400 mg/day [59].

Traditional stimulants, such as methylphenidate and amphetamines, act via dopamine and NE reuptake inhibition and are highly effective at promoting wakefulness. However, they carry greater risk of side effects, including insomnia, appetite suppression, tachycardia, and potential misuse, and require cautious dosing (10 - 60 mg/day) [34].

Pitolisant (Wakix), a histamine H3 receptor antagonist, is approved for narcolepsy and has shown promise in IH by enhancing histaminergic neurotransmission to promote wakefulness. Though not yet FDA-approved specifically for IH in the U.S., European studies and open-label trials suggest benefit in reducing sleepiness. Pitolisant is generally well tolerated but may cause insomnia, headache, or anxiety at typical doses of 17.8 - 5.6 mg/day [60].

Clarithromycin, a macrolide antibiotic with negative allosteric modulatory effects on $GABA_A$ receptors, may improve EDS in a subset of IH patients. It is conditionally recommended for adult IH based on low- certainty evidence, with modest subjective improvement in sleepiness, inconsistent objective benefit, and potential $GABA_A$ antagonism. Use should be individualized due to gastrointestinal side effects, QT prolongation, drug interactions, and antibiotic stewardship concerns. Doses range from 250 - 500 mg/day [61].

Summary

IH is a chronic central hypersomnolence disorder that impairs daily functioning and quality of life. Lacking definitive biomarkers, IH is frequently misdiagnosed or mistaken for psychiatric conditions. Diagnostic challenges include the limited specificity of the MSLT in distinguishing IH from NT2. Accurate diagnosis requires exclusion of other causes and objective evaluation with actigraphy or extended PSG. Evidence of GABAergic dysfunction suggests potential biomarkers. Low-sodium oxybate improves sleepiness and inertia but remains difficult to access. Ongoing research aims to refine biomarkers and optimize individualized care.

Acknowledgements

None.

Conflict of Interest

None.

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