

# Idiopathic Hypersomnia

Diksha Gupta<sup>1\*</sup> and Trisha Chatterjee<sup>2</sup>

<sup>1</sup>Amity Institute of Pharmacy, Amity University, India

<sup>2</sup>Department of Biotechnology, Amity University, India

## Review Article

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### \*For Correspondence

Gupta D, Amity University, Noida, UP, India, Tel: 8588829759.

**E-mail:** diksha.gupta19@yahoo.in

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### ABSTRACT

Sleep is an unconsciousness form by which the person could be aroused by sensory or other stimuli. These days due to psychological and social dysfunction our daily routine affects the quality of our life, according to survey much health related issues are being reported due to lack of sleep. An ancient literature review was given and explained the theory about the leading symptom of idiopathic hypersomnia was sleep drunkenness and the first patient was thus diagnosed with prolonged nocturnal sleep accompanied by excessive daytime sleepiness with long naps and difficult awakening. A severe issue with this disease is that most people tend to suffer from "Depression". Due to ischemic changes along the border of mesencephalon and diencephalon and post-traumatic etiology in other, people thus suffer from "sleep drunkenness". The term idiopathic hypersomnia was given a variety of clinical labels including idiopathic central nervous hypersomnia or hypersomnolence, functional hypersomnia, mixed or harmonious hypersomnia, hypersomnia with automatic behavior, and non-rapid eye movement (NREM) narcolepsy. Two different clinical forms were recommended —idiopathic hypersomnia with long sleep time and IH without long sleep time which then reappeared in the latest International Classification of Sleep Disorders. However, the biological background of these clinical entities remains unknown, and much effort is needed to shed more light on its pathophysiology.

## INTRODUCTION

It is considered that a person who might be aroused from an apparently unconsciousness state through some type of stimuli including sensory stimulation can be termed as "Sleep" [1]. There are multiple stages of sleep, i.e., very light sleep to very deep sleep researchers also divide sleep into two entirely different types of sleep that have different qualities, as follows. Every night a person passes through these stages of sleep which alternate with each other. They are known as (i) slow wave sleep: this is the restful phase in which the brain waves are very strong and of very low-frequency. In this the phase there are a lot of chances of the decrease in blood pressure, respiratory rate, and metabolic rate. (ii) Rapid eye movement sleep: it is the non-restful sleep which occurs in rapid episodes it can only occupy 25% of sleep in adults. Due to lack of sleep in our daily routine people are facing many disorders which can interfere with the normal, physical mental and social and emotional well-being. They are the mostly epidemic affecting disorders affecting almost every age group from infant to old. Due to these sleep disorders; it can lead to various risks like obesity, high blood pressure, heart disease, stroke, diabetes, depression, and unexplained sudden death. Many accidents and disasters have occurred because of improper mental health due to lack of sleep. For example, the infamous Exxon Valdez oil spill tragedy that affected our planet's wildlife and ecosystem off the coast of Alaska in 1989 was likely a result of cloudy judgment related to sleep deprivation. Other examples of disasters at least partially attributed to sleep deprivation or disorders include the chemical accident at the Union Carbide plant in Bhopal, India, the nuclear accident at Chernobyl in Ukraine, and the nuclear accident at Three Mile Island in 1979 [2]. There are types of disorders which like: (i) Bruxism: grinding of teeth during sleep. As teeth grinding has become a major concern for dentists because of its consequences. Problems such as tooth wear, fracture of dental restorations, periodontal problems, and exacerbation of temporomandibular disorders, stress

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induction leading to headaches, and grinding sounds may interfere with the sleep of family members. To cure this problem doctor recommended reducing or eliminating caffeine and carbonated drink consumption in daily routine and stress counseling <sup>[3,4]</sup>. Insomnia: severe problem in falling asleep. Chronic type of insomnia is Psychophysiological insomnia (PPI) and is most common in sleep setting. Few factors that lead to PPI are somatization tension, psychic interaction, anxiety, and depression. To prevent all these factors, proper sleep and hygiene instructions should be followed. Mostly it occurs in adults around the mid-30s and above. According to various surveys, in most cases, it affects men. Insomnia is also a major cause of post-menopausal issues in women. A report of difficulty in initiating sleep, maintaining sleep, or experiencing no restorative sleep, despite adequate opportunity for sleep is usually reported in women. Daytime functional impairments resulting from nocturnal sleep disturbance have also been reported <sup>[5-7]</sup>, (iii) Obstructive sleep apnea: obstruction in the air passage during sleep which causes snoring. Obesity is a major risk factor. However, its pathogenesis is complex and multifactorial. Reduced upper airway muscle tonus and/ or unstable neuromuscular output seem to be involved in this collapse. Patients with OSA usually suffer from following problems: a morning headache, nocturia, lethargicness, poor concentration and memory impairment. Recently some hematological parameters as red cell distribution width (RDW), mean platelet volume (MPV), and platelet distribution width (PDW) have been emerged as inflammatory biomarkers <sup>[8-10]</sup>. Few of the rare disease about which society is less aware and no proper treatment are found they are the following: Narcolepsy, Idiopathic hypersomnia. (i) Narcolepsy: A chronic neurological disorder (or dysomnia), which is caused by the brain's inability to control sleep and wakefulness, whereas, (ii) Idiopathic hypersomnia: a chronic neurological disease similar to narcolepsy in which there is an increased amount of fatigue and sleep during the day. Patients who suffer from idiopathic hypersomnia cannot obtain a healthy amount of sleep for a regular day of activities. This hinders the patients' ability to perform well, and patients have to deal with this for the rest of their lives. These two diseases have many symptoms in common differentiating them is a little difficult task. So, will throw some light on, how idiopathic hypersomnia can be different from narcolepsy and what are the causes and treatments for this?

### Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is a neurological disorder in which a person experiences excessive daytime sleepiness (EDS). The history of idiopathic hypersomnia is different from that of narcolepsy which is rarely known. Idiopathic hypersomnia was first termed by Henrich Bruno Schindler for excessive daytime sleepiness because of its undetermined origin. Bedrich Roth determined the clinical differences between narcolepsy and other types of hypersomnias. His theory suggested that this disease mostly occurs at the age of 15 to 33 years. He also found that "sleep drunkenness" is the main clinical symptom of IH. He found that sleep drunkenness is a symptom which is connected with prolonged nocturnal sleep and shows difficulty in awakening. The main symptom which usually occurs in patients diagnosed with this disease is "Depression". According to literature a cause in sleep drunkenness and prolonged deep nocturnal sleep, which are the ischemic changes along the borderline between the mesencephalon and diencephalon in one case and post-traumatic etiology in other. As it is a lifelong chronic disease it makes a person weak and infirm. In idiopathic hypersomnia, there appears to be an overproduction of a small molecule which acts like a sleeping pill. The exact composition of this molecule is yet to be determined, but it is known to interact with  $\gamma$ -aminobutyric acid (GABA), which plays a major role in the brain mechanisms, that promotes sleep. In the presence of this compound, the inhibitory and sleep promoting actions of GABA are enhanced at the receptors. People suffering from narcolepsy type 1 can easily be differentiated from people suffering from narcolepsy type 2 and hypersomnia since narcolepsy type 1 have clearly distinguished symptoms whereas for narcolepsy type 2 and hypersomnia the symptoms can often overlap significantly. A common question often asked by sleep disorder patients is that how much sleep and sleepiness is normal? According to surveys around 8% of people sleep for more than 9 hours per day, and 1.6% of people report sleepiness which disrupts their waking activities. One of the most useful tests is the Multiple Sleep Latency Test. Studies have shown that 71% of people with long sleep times and other symptoms of IH, had a mean sleep latency of more than 8 minutes. Research from Emory University has shown that around 50% of people with chronic fatigue syndrome meet the MSLT criteria for IH. The International classification of sleep disorders (ICSD-1) in 1990 explained idiopathic hypersomnia may be a CNS-based disorder related with normal or prolonged i.e., 1-2 h cycles of NREM (non-rapid eye movement) sleep. The two disorders "narcolepsy" and "hypersomnia" were divided into the subgroup of dysomnias which give rise to following symptoms: excessive sleepiness, insomnia and also referred as intrinsic sleep disorders.

### Causes

The most common reason of excessive sleepiness is obstructive sleep apnea. Mostly People with Obstructive Sleep Apnea (OSA) struggle with breathing problem during the night time resulting in waking up a number of times during the night. This continuous waking up disrupts the natural sleeping cycle and as a result, the person doesn't have sufficient and healthy sleep and feels drowsy the next day. Many people with OSA do not realize that they have it because they wake up briefly and believe that they have slept continuously throughout the night. If you are excessively sleepy during the day and snore, have high blood pressure or are overweight chances are that you are suffering from Obstructive Sleep Apnea. The other cause may be due to the destruction of noradrenergic neurons which produces hypersomnia while experimenting on animals, and injury to adrenergic neurons has also been shown to lead to hypersomnia. Idiopathic hypersomnia has also been associated with a malfunction of the norepinephrine system and decreased cerebrospinal fluid (CSF) histamine levels. It is currently referred to as a "somnogen" because it has been shown to cause hyper-reactivity of GABAA receptors, which leads to increased sedation or somnolence. In essence, it is as though these patients are chronically sedated with a benzodiazepine (medication which acts through the GABA system) such as Versed

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or Xanax, even though they do not take these medications but the team at Emory were testing cerebrospinal fluid levels of GABA potentiation in everyone with hypersomnia at one point, they are not doing this routinely at the moment and have found that people with sleepiness due to other causes such as sleep apnea can also have GABA potentiation, meaning that what they had previously described as a "somnogen" may not be specific for IH but may, in fact, be a mediator of sleepiness symptoms in a range of conditions.

### Epidemiology

According to surveys, IH % reported is 5-15% of individuals who mostly complaints about daytime sleepiness, it appears to be a lifelong condition. Spontaneous remission is only seen in 10-15% of patients<sup>[11,12]</sup>. According to the limited epidemiological data that exists, IH "has more of a female preponderance (1.8/1)<sup>[13]</sup> Family cases are frequent, in a range from 25% to 66% without any clear mode of inheritance<sup>[14]</sup>. As it is a rare disease and has not received any special attention by authorities and researchers. In Europe and in North America there is now a public health concern about helping patients and families affected by these rare diseases. Due to the complexity of the disease, they often experience difficulties to be diagnosed and often face social and professional consequences<sup>[15]</sup>. A study by Ohayon et al. suggested that excessive sleepiness is more prevalent than previously estimated. The study found that with 27.8% of 15,929 individuals from 15 US states reported excessive sleepiness. Even when using restrictive criteria of frequency at least 3 times per week for at least 3 months despite normal sleep duration, the prevalence was 4.7%. The diagnosis of idiopathic hypersomnia is complicated by the fact that differentiating between excessive versus long sleep or normal versus abnormal wakefulness is often difficult. Based largely on sleep center referrals, idiopathic hypersomnia appears to be one-tenth to one-half as common as narcolepsy, suggesting a prevalence of approximately 20 to 50 cases per million<sup>[1]</sup>. There is no clear gender association. The onset of idiopathic hypersomnia typically occurs between 10 and 30 years of age. In a series of 77 patients, the mean age of symptom onset was 17 and the mean age at diagnosis was 30.

### Signs

Symptoms often develop slowly during teenage. They included (i) Daytime naps that do not relieve drowsiness. (ii) Difficulty waking from a long sleep may feel confused or disoriented ("sleep drunkenness"). (iii) Increased need for sleep during the day, even while at work, or during a meal or conversation. (iv) Increased sleep time – up to 14 to 18 hours a day. Other symptoms may include: anxiety, feeling irritated, loss of appetite, low energy, restlessness, slow thinking or speech, trouble remembering, depression, certain medicines, drug and alcohol use, low thyroid function, previous head injury.

### Varieties of Signs

Multidimensional Fatigue Inventory – measure of fatigue, Short-form Beck Depression Inventory – measure of depression, Horne-Östberg Scale – measure of circadian phase, Psychomotor Vigilance Test – measure of alertness and response times. There really wasn't any clear consensus on how exactly to define hypersomnia and IH. Unfortunately, there are not good biological markers, and trying to make a definite diagnosis based on symptoms is fraught with difficulty. So an approach put forward by the team from Emory and that seems to make sense is to try to exclude other factors that can be added to sleepiness symptoms, such as depression and circadian rhythm disorders, as well as getting a number of objective measurements of sleepiness and its impact<sup>[16]</sup>.

### Diagnosis

Earlier we have found that it was very difficult to distinguish the symptoms of EDS as idiopathic hypersomnia, such as for example, upper airway resistance syndrome and delayed sleep phase disorder. The symptoms of these disorders were similar to idiopathic hypersomnia. Many specific treatments were failed to suppress the effects of EDS. By the use of few subjective scales and objective test the severity of EDS can be measured or detected. Epworth sleepiness scale and Stanford sleepiness scale are an example of such scale and by performing the multiple sleep latency tests. In 2001, the ICSD (International Classification of Sleep Disorders) updated their criteria for the diagnosis of idiopathic hypersomnia as follows: EDS must be present for minimum 3-6 months, certain characteristics must be shown by sleep studies i.e., polysomnography and MSLT. As these processes are very tedious, time-consuming and expensive for the patients. A Multiple Sleep Latency Test (MSLT) performed according to standard techniques shows fewer than two sleep-onset REM periods or no sleep-onset REM periods if the REM latency on the preceding polysomnogram was less than or equal to 15 minutes. The presence of at least one of the following: (i) The MSLT shows a mean sleep latency (MSL) of  $\leq 8$  minutes. (ii) Total 24-hour sleep time is  $\geq 660$  minutes (typically 12–14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation) or by wrist actigraphy in association with a sleep log (averaged over at least seven days with unrestricted sleep). (iii) Insufficient sleep syndrome is ruled out (if deemed necessary, by the lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed (preferably confirmed by at least a week of wrist actigraphy). (iv) The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications<sup>[16]</sup>.

### Treatment

For the treatment of IH, the renewed medications are being consumed by patients. On basis of reports shows that around 50% of people were earlier consuming modafinil but now due to lack of its efficacy they are not continuing with the treatment.

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Only a few people around 30%-60% consuming dexamphetamine". Other medicines used are- (i) CLARITHROMYCIN: this was used by the team of Emory in 2015 and they published their research in "annals of neurology". The research was being done on 23 people but the results were reported of 20 cases by giving 500mg twice daily. Therefore, no changes in reaction time were being shown but significantly subjective measures of sleepiness were improved. The side effects were reported are GIT side effects, change in taste. So, it was not that clear about its use and effect but can be a helpful agent. (ii) FLUMAZENIL: this was also used by Emory team. They showed the results which they performed on 153 patients between 2013-2015. They administered the drug as sublingual lozenges or transcutaneous lotion. The percentage data shows that about 63% of people find it useful for their sleepiness, by dropping the Epworth sleepiness score. Around 39% of people remained on treatment till the observation period which was of 7.8 months. Around 72% of people show the presence of significant sleep inertia and remaining 42% were without sleep inertia. (iii) SODIUM OXYBATE (XYREM): is another treatment used for sleep inertia the most difficult symptom in hypersomnia. This medication is commonly used to treat narcolepsy. A number of people were treated with this medication in Paris by a researcher "Isabelle Arnulf". The results were shown that it can reduce sleep inertia. It may improve quality of life but studies indicate some patients fail to respond or find the treatment unacceptable due to side effects (e.g. nausea and vomiting, anorexia and dizziness)<sup>(47)</sup> (iv) JZP-110: this medicine has dopaminergic and noradrenergic activity and 2 small clinical trials were conducted on total 126 subjects, it was seen to increase the Multiple Sleep Latency on a Maintenance of wakefulness test by 8.9 minutes as in comparison to modafinil studies MSL was increased by 2.3 minutes and with dexamphetamine, there is an increase of MSL by 5.6 minutes. Therefore, according to results JZP-110 is significantly more effective than other drugs. (iv) NON-DRUG TREATMENTS: medication can only treat symptoms but the patients dealing with hypersomnias the majorly they are affected psychologically. The behavioral treatments should be done to reduce the impact of symptoms on people and other conditions that can cause sleepiness. Napping is the easy way to treat narcolepsy with cataplexy but for people suffering from idiopathic hypersomnia napping does not work as they could not have short naps and have significant sleep inertia on waking up from naps. To manage symptoms of sleepiness research on behavioral strategies are in process.

### CONCLUSION

Idiopathic hypersomnia is the rare disease which needs a serious attention of the authorities and the researchers in comparison to narcolepsy it is 10 times less frequent. The complexity of this disease, patients and families often experience difficulties during diagnosis and face professional and social consequences. There is more demand for public awareness is required. The improper lifestyle of sleeping due to work pressure and depression due to the different situation leading to the cause of this problem disease. Since JZP-110 is till now the effective drug but similarly psychological behavioral treatments will reduce the impact of symptoms. Therefore, patients with idiopathic hypersomnia need emotional support because they are at risk of being misunderstood as being unprofessional or inactive. So, awareness among relatives, friends, and colleagues helps the patient to perform and improve much better with this incurable disease.

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