Update on hypersomnias of central origin

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\textbf{Purpose of review}
To describe the multiple clinical aspects of hypersomnias of central origin. Emphasis is given to the new pathophysiological pathways and treatment options described in the current literature.

\textbf{Recent findings}
Narcolepsy is the most recognized of the hypersomnias of central origin. Hypocretin deficiency appears to underlie narcolepsy with cataplexy, and infections and vaccinations have been associated with disease onset. Targeted therapeutic approaches are currently underway. A putative naturally occurring constituent in the cerebrospinal fluid of patients with non-narcoleptic primary hypersomnias, able to stimulate \(\gamma\)-aminobutyric acid alpha receptors and induce sleep, has recently been postulated. Neuroimaging has also provided more insight into the pathophysiology of Kleine–Levin syndrome. Sleep deprivation is currently recognized as a major differential diagnosis.

\textbf{Summary}
Excessive daytime sleepiness is the cardinal symptom of the hypersomnias of central origin, with major impact on the quality of life. It is important that clinicians be able to recognize these conditions, so that appropriate management or onward referral is expedited.

\textbf{Keywords}
behaviourally induced insufficient sleep syndrome, cataplexy, idiopathic hypersomnia, Kleine–Levin syndrome, narcolepsy

\section*{INTRODUCTION}
Excessive daytime sleepiness (EDS) is common, and may have severe and wide-ranging consequences. Most frequently, EDS is the result of sleep breathing disorders, other causes of disturbed nocturnal sleep and circadian rhythm problems. If these are appropriately excluded or treated and the complaint still persists, then the diagnosis of hypersomnia of central origin emerges.

Although their prevalence compared with sleep breathing disorders is low, it is important for the clinicians to be able to recognize and treat these conditions appropriately \cite{1,2}. The current estimate of mean time from the onset of symptoms to the diagnosis for narcolepsy, the most readily recognizable of these conditions, is 10 years \cite{3}.

The hypersomnias of central origin include both primary and secondary hypersomnias as classified in the International Classification of Sleep Disorders, 3rd edition (ICSD3) \cite{4} (see list below).

Hypersomnias of central origin are classified as follows \cite{4}:

1. narcolepsy type 1 [narcolepsy with cataplexy or deficit of cerebrospinal fluid (CSF) hypocretin];
2. narcolepsy type 2 (narcolepsy without cataplexy or evidence of deficiency of CSF hypocretin);
3. idiopathic hypersomnia;
4. Kleine–Levin syndrome (KLS);
5. insufficient sleep syndrome;
6. hypersomnia because of a medical disorder;
7. hypersomnia because of a medication or substance;
8. hypersomnia associated with a psychiatric disorder.

\section*{NARCOLEPSY}
Narcolepsy represents the classic hypersomnia of central origin, and is the best understood of these conditions.

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Clinical features
Narcolepsy is characterized by the symptom tetrad of EDS, hypnagogic hallucinations, sleep paralysis and cataplexy [4**]. However, only 10–15% of patients have all four symptoms. The only mandatory feature is EDS, ranging from frank sleep attacks to constant sleepiness with occasional exacerbations. Usually, patients fall asleep for seconds or minutes, but may be more prolonged, especially following sudden withdrawal orders, sleep restriction should be excluded with polysomnography (PSG) to exclude other sleep disorders, sleep restriction should be excluded with sleep diaries or 2 weeks of actigraphy prior to the study and patients should be off all drugs that might influence the results of the MSLT for 2 weeks [4**] (see list below).

Diagnostic testing
The multiple sleep latency test (MSLT) remains the major diagnostic test for narcolepsy. However, it is a biological test with a high false-positive and false-negative rate; it should be undertaken after full polysomnography (PSG) to exclude other sleep disorders, sleep restriction should be excluded with sleep diaries or 2 weeks of actigraphy prior to the study and patients should be off all drugs that might influence the results of the MSLT for 2 weeks [4**] (see list below).

ICSD3 diagnostic criteria for narcolepsy [4**] are as follows:

Pathophysiology
A strong genetic component is indicated by the familial studies that show the risk of developing narcolepsy with cataplexy (N+C) in a first-degree relative is 1–2% [16]. A strong association with the human leucocyte antigen (HLA) has been demonstrated, especially with the HLA DQB1*0602 haplotype [17*]. There are also suggestions of infective triggers, supported by high serum titres of antistreptolysin O antibodies, and more recently, the H1N1 swine flu virus or vaccination has been linked to narcolepsy [18,19,20*,21,22,23*,24,25]. Unfortunately, the most convincing experimental evidence for this link [19] has very recently been retracted due to inability to replicate findings.

Further research has revealed the role of hypocretin and orexin transmission in the pathogenesis of narcolepsy. Patients with N+C show a loss of some or all of the 70 000 hypocretin-producing neurones in the lateral hypothalamus, resulting in inherent instability in the neural network responsible for maintaining wakefulness and preventing REM sleep [23*,26,27]. The hypothesis in humans is that there is a genetic predisposition to autoimmune attack of the hypocretin-producing neurones in the lateral hypothalamus, triggered by the environmental factors such as infective agents [28–30].

Key points
- Excessive daytime sleepiness is the mandatory common feature of hypersomnias of central origin. Its consequences are profound and raised clinical awareness is necessary to avoid significant diagnostic delay.
- The diagnosis of hypersomnias of central origin is largely clinical, and diagnostic tools should play a supportive role.
- Narcolepsy is not rare, with a prevalence of about one in 3000; its typical onset is in adolescence or middle age.
- New insights into the pathophysiology of EDS are giving rise to novel therapeutic approaches.
narcolepsy type 1
(a) The patient has daily periods of irresistible need to sleep or daytime lapses into sleep occurring for at least 3 months.
(b) The presence of one or both of the following:
(i) Definite cataplexy and a positive MSLT (mean sleep latency of 8 min or less and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREM (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREM's on the MSLT.
(ii) Cerebrospinal fluid (CSF) hypocretin-1 concentration, measured by immunoreactivity, is either 110 pg/ml or less than one-third of the mean values obtained in normal individuals with the same standardized assay.

2. narcolepsy type 2:
(a) The patient has daily periods of irresistible need to sleep or daytime lapses into sleep occurring for at least 3 months.
(b) Positive MSLT (mean sleep latency of or less 8 min and two or more SOREM's on an MSLT performed according to standard techniques. A SOREM (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREM's on the MSLT.
(c) Cataplexy is absent.
(d) Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either greater than 110 pg/ml or greater than one-third of mean values obtained in normal subjects with the same standardized assay.
(e) The hypersomnia/ence and MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

Nevertheless, there are additional features of both the polysomnography and MSLT that make narcolepsy more likely, such as REM sleep arising from wake or stage 1 of non-REM (NREM) sleep in the first REM period of the night, or in the daytime naps [31*,32].

Increased emphasis has been given to CSF hypocretin-1 levels as part of the diagnostic workup. A low CSF hypocretin-1 confirms the diagnosis of narcolepsy with or without cataplexy, but a normal CSF hypocretin-1 does not help in diagnosing narcolepsy without cataplexy. Changes to the diagnostic criteria for narcolepsy in the recently published ICSD3 divides narcolepsy into those patients with cataplexy and low or deficient CSF hypocretin-1 levels, and those without cataplexy and normal hypocretin-1, implying that many of those without cataplexy but abnormal hypocretin will go on to develop cataplexy later in the disease course [4**].

In contrast, HLA typing has a very limited clinical use, except for those with N+C, in whom a positive test is no more useful than a history of typical cataplexy. However, 98% of patients with a low CSF hypocretin-1 are DQB1 ‘0602 positive, and so testing for the haplotype may have a role in those patients in whom a lumbar puncture is being considered for diagnostic clarification.

Management
Planned short naps can be sufficient to establish reasonable control in some patients, but pharmacotherapy is usually required. The mainstays of drug treatment for EDS are the stimulants (Table 1). Modafinil is the best tolerated of these, with a good safety profile [33]. Like other stimulants, it not only increases monoamine release, but also elevates hypothalamic histamine levels, and is considered a ‘wake-promoter’ rather than an amphetamine-like stimulant [34*]. Methylphenidate and dexamphetamine are amphetamines with a higher rate of adverse events, especially hypertension and psychiatric effects. Alternative agents for treating EDS include selegiline, mazindol and nicotine [35]. Atomoxetine is also beginning to be used in narcolepsy, although the experience is very limited [34*].

Cataplexy may respond to methylphenidate or dexamphetamine, but more usually requires specific antiscataplectic agents. Clomipramine and venlafaxine are the standard treatments, and the choice largely depends on other features of narcolepsy; clomipramine may help night-time insomnia, and venlafaxine can provide an additional stimulant effect. Fluoxetine is an alternative antiscataplectic agent [34*].

Sodium oxybate is a novel drug that is effective for the treatment of cataplexy and EDS [36]. It is a γ-aminobutyric acid beta (GABA) agonist, although its mechanism of action is not entirely understood. It also acts as a respiratory depressant and deaths have occurred in combination with alcohol or other central nervous system depressant drugs [34*].

Suppression of the presumed immune-mediated attack on hypocretin-producing neurones with
<table>
<thead>
<tr>
<th>Drugs for excessive daytime sleepiness</th>
<th>Duration of action</th>
<th>Typical starting dose</th>
<th>Usual maintenance dose</th>
<th>Frequent side-effects</th>
<th>Serious side-effects</th>
<th>Cautions</th>
<th>Comments</th>
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<tr>
<td>Modafinil</td>
<td>8–16 h</td>
<td>100 mg o.d.</td>
<td>100–400 mg/day in one or two doses, with latest dose before 2 p.m.</td>
<td>Headache, nausea, gastrointestinal upset, anxiety, insomnia, palpitations, aggression</td>
<td>Drug rash including Stevens–Johnson Syndrome, anaphylactoid reactions, hypertension</td>
<td>Avoid in patients with left ventricular hypertrophy or mitral valve prolapse. Potential interaction with hormonal contraceptives</td>
<td>Low potential for abuse. Can be used in conjunction with amphetamines</td>
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<tr>
<td>Methylphenidate</td>
<td>3–4 h normal release preparation</td>
<td>5 mg b.i.d.</td>
<td>10–60 mg/day in 2–3 divided doses 100–108 mg once-daily, depending on brand</td>
<td>Anxiety, tremor, palpitations, weight loss, gastrointestinal upset, dry mouth</td>
<td>Hypersensitivity reactions, depression, hypomania, psychosis, hypertension, reduced seizure threshold, arrhythmias</td>
<td>Avoid in severe psychiatric disease, cardiovascular disease, cerebrovascular disease and phaeochromocytoma</td>
<td>Potential for abuse. Mild anticytaphetic activity</td>
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<tr>
<td>Dexamphetamine</td>
<td>6–10 h</td>
<td>5–10 mg daily in one or two doses</td>
<td>10–60 mg per day in two doses</td>
<td>Dizziness, anxiety, flushing, dry mouth, headache, blurred vision, gastrointestinal upset, weight loss</td>
<td>Hypersensitivity reactions, seizures, arrhythmias, paranoia, psychosis, withdrawal effects, cerebral vasculopathy</td>
<td>Contraindicated in severe hypertension, structural cardiac abnormalities, advanced atherosclerosis, previous substance abuse. Contraindicated with MAOIs</td>
<td>Significant potential for abuse. Mild anticytaphetic activity</td>
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<tr>
<th>Drugs for cataplexy</th>
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<tr>
<td>Clomipramine</td>
<td>10 mg nocte</td>
<td>10–75 mg nocte</td>
<td>Antimuscarinic side-effects, postural hypotension, confusion, sedation, agitation, weight gain</td>
<td>Arrhythmias, heart block, suicidal behaviour, myoclonus, allergic alveolitis</td>
<td>May be helpful with prominent nighttime insomnia. Can exacerbate PLMD</td>
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(Continued)
intravenous immunoglobulins within the first few weeks of onset in N+C has been reported as producing persistent clinical improvements, but these findings have not been consistently reproduced [37]. Other experimental agents include clarithromycin, which has shown some preliminary promising results in patients with narcolepsy without hypocretin deficiency, and is presumed to act by modulating central γ-aminobutyric acid alpha (GABA_α) receptor hyperactivity [38]. Hypocretin agonists have also been proposed to treat narcolepsy in hypocretin neurone-ablated mice, but no hypocretin agonist small enough to cross the blood–brain barrier currently exists [39,40]. Other potential novel therapies being explored include histamine antagonists and melanin-concentrating hormone receptor antagonists [41,42].

**IDIOPATHIC HYPERSOMNIA**

Idiopathic hypersomnia is a relatively recently described condition, and the lack of laboratory tests combined with the vague clinical spectrum of the syndrome make diagnosis problematic [43].

**Clinical features**

No appropriate prevalence studies for idiopathic hypersomnia exist so far. A ratio of one to two patients with idiopathic hypersomnia for every 10 with narcolepsy has been proposed, with both sexes equally affected [44]. At diagnosis, most patients have had the disorder for many years, and age of onset is usually during adolescence or the early 20s.

Idiopathic hypersomnia is no longer classified according to the duration of night sleep; more than 11 h of sleep are now expected, otherwise clinical judgment should be used in deciding whether these patients should be considered to have idiopathic hypersomnia. One of the notable characteristics of idiopathic hypersomnia is sleep drunkenness, which is the difficulty achieving full alertness on waking from night sleep or a nap, despite a normal total sleep time. Unrefreshing naps tend to last longer than in narcolepsy, up to 4 h. Depressed mood also may be observed, without fulfilling the criteria for mood disorder [45]. Furthermore, headaches, fainting episodes and other symptoms suggesting dysfunction of the autonomic nervous system are not uncommon.

**Pathophysiology**

The cause of idiopathic hypersomnia remains mostly speculative, and dysfunction of the norepinephrine system, melatonin secretion and a
circadian dysfunction have all been postulated [46]. An association with the hypocretin–orexin system, hypothalamic dysfunction and an abnormal homeostatic sleep drive has also been proposed, but evidence in this regard is lacking [47]. Recently, it has been demonstrated that CSF from patients with non-narcoleptic primary hypersomnia possibly contains a small endogenous substance that potentiates the effects of GABA on in-vitro function of selected GABA<sub>A</sub> receptors. Thus, a novel pathophysiological mechanism for EDS for these patients may have been identified [48**]. Finally, no clear genetic predisposition has been identified, even though the familial cases of idiopathic hypersomnia have been observed.

**Diagnostic issues**

Idiopathic hypersomnia is a diagnosis of exclusion and is based primarily on the clinical features. Importantly, behaviourally induced insufficient sleep syndrome (BIISS) is an important mimic of idiopathic hypersomnia with short sleep time. Polysomnography and MSLT are mandatory in the diagnosis of idiopathic hypersomnia, with clear diagnostic criteria (see list below). In practice, however, there remain concerns about the sensitivity of the MSLT in this condition [49]. ICSD3 diagnostic criteria for idiopathic hypersomnia [4**] are as follows:

1. The patient has daily periods of irrepresible need to sleep or daytime lapses into sleep occurring for at least 3 months.
2. Cataplexy is absent.
3. An MSLT performed according to the standard techniques shows less than two SOREMPs or no SOREMPs if the REM latency on the preceding polysomnogram was 15 min or less.
4. The presence of at least one of the following:
   a. The MSLT shows a mean sleep latency of 8 min or less.
   b. Total 24-h sleep time is at least 660 min (typically 12–14 h) on 24-h polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).
5. Insufficient sleep syndrome is ruled out (if deemed necessary, by 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).
6. The hypersomnolence and MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

The proposed treatments for idiopathic hypersomnia are similar to those utilized in narcolepsy, but the response to medication is variable. Recently published data supports the effectiveness of the benzodiazepine receptor antagonist flumazenil in patients with idiopathic hypersomnia and previous treatment failure [48**,50]. The possible important role of GABA<sub>A</sub> receptors in EDS has also been suggested by the tantalizing results of using clarithromycin, presumed to be mediated through these receptors [38].

**RECURRENT HYPERSOMNIAS**

The recurrent hypersomnias comprise a range of conditions resulting in bouts of intermittent sleepiness without symptoms in between bouts.

**Kleine–Levin syndrome**

KLS is a classic but very rare cause of recurrent hypersomnia, with an estimated prevalence of one in a million. It is characterized by the sudden occurrence of recurrent episodes of marked hypersomnia. About 50% of patients exhibit hyperphagia and hypersexuality. Depressed mood, anxiety and hallucinations may also be found (see list below).

ICSD3 diagnostic criteria for recurrent hypersomnia (KLS and menstrual-related EDS) [4**] are as follows:

1. The patient experiences at least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks.
2. Episodes recur usually more than once a year and at least once every 18 months.
3. The patient has normal alertness, cognitive function, behaviour and mood between episodes.
4. The patient must demonstrate at least one of the following during episodes:
   a. cognitive dysfunction;
   b. altered perception;
   c. eating disorder (anorexia or hyperphagia);
   d. disinhibited behaviour (such as hypersexuality);
5. The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.

The onset of the syndrome usually occurs during adolescence (81%) but may occur at any age. Its prevalence is higher in the Ashkenazi Jewish population compared with other ethnicities [4**,47,51].
No clear genetic basis for KLS has been found, although familial cases have been described. CSF hypocretin has been found low during the hypersomnic episodes compared with baseline, but these findings are not at all consistent. A recently published review of the case report studies described traumatic brain injury (TBI) as a potential trigger of KLS, acting together with fever, stress, alcohol, or heat in a genetically predisposed individual to trigger recurrent hypersomnia [52]. More recently, imaging techniques have suggested a diminished connectivity between the brainstem and the thalamus during an active KLS episode, and widespread brain hypermetabolism in symptomatic and asymptomatic episodes of KLS, but the significance of these changes remains uncertain [53,54]. It must be emphasized that KLS remains a clinical diagnosis.

Various treatments have been tried in patients with KLS. Only a limited number of the patients have demonstrated an improvement using preventive strategies, such as lithium, carbamazepine, valproic acid, amantadine, risperidone and lamotrigine. During episodes, stimulants have occasionally shown some benefit, but no treatment option has demonstrated consistent results [55].

Menstrual-related hypersomnia
Menstrual-related hypersomnia (MRH) is characterized by recurrent episodes of hypersomnia correlated with menstrual cycle in women and shares same diagnostic criteria with KLS (see list above). It is a rare condition and there are no data supporting it as a hereditary trait. A recent review describes that the onset of hypersomnolent episodes may occur either in menarche, puerperium and during menstruation, with or without the co-occurrence of other trigger factors like influenza or alcohol. Dysautonomic features were identified in 24% of patients with MRH, and weight gain and depression were also prominent in this group [56]. Treatment approaches include inhibition of ovulation through the use of progesterone-only contraception, but this is only supported by case reports.

BEHAVIOURALLY INDUCED INSUFFICIENT SLEEP SYNDROME
BIISS is a newly defined hypersomnia, characterized by EDS, with a short habitual sleep duration and sleeping considerably longer during weekends in order to catch up on sleep. Sleep deprivation is the cause of BIISS and there is supporting evidence that its prevalence is very high because of the current lifestyles. It is most commonly seen amongst adolescents and history is the basis for the diagnosis. A short sleep-onset latency, high sleep efficiency and high proportion of NREM3 sleep are likely to be demonstrated on PSG. SOREMPs may occur during the MSLT or during PSG, but these are unlikely to arise from NREM1 or wake [31*,32]. Extension of the sleep opportunity with sleep hygiene measures is the appropriate management approach.

HYPERSOMNIA BECAUSE OF OTHER CAUSES
Hypersomnia may be attributed to a wide variety of medical conditions such as metabolic syndromes, infections, toxins and drugs. Parkinson’s disease, myotonic dystrophy and rarer disorders such as Prader–Willi syndrome and Niemann–Pick type C disease are associated with the development of hypersomnia, and indeed some degenerative neurological disorders may precipitate a symptomatic narcolepsy with associated cataplexy. Other potential causes of symptomatic narcolepsy include hypothalamic tumours, Wernicke’s encephalopathy, multiple sclerosis, Devic’s disease and autoimmune encephalitides. TBI is a frequent cause of a central hypersomnia, particularly with posterior hypothalamic damage. Prescribed and illicit drugs should be considered as a potential cause for unexplained hypersomnia, particularly the opiates. Recently, awareness has been raised regarding the possible causality connection of H1N1 swine flu virus or vaccination administration in children and the development of secondary narcolepsy [18,20*,24,57]. EDS can be a feature of major depression and if the cause of hypersomnia remains vague even after the consideration of the aforementioned causes, patients should be assessed for the possible psychiatric disorders as well.

CONCLUSION
During recent years, an increased understanding of the pathophysiology of narcolepsy has been achieved, although many of the other central hypersomnias remain poorly understood. With the exception of CSF hypocretin-1 measurement, diagnostic tools remain of limited value, and many of the hypersomnias of central origin remain clinical diagnoses of exclusion. Clinicians need to be aware of the limitations of the current diagnostic tools and should view these as an extension of the clinical picture rather than a gold standard.

Acknowledgements
None.
The association between HLA-DQB1 utilization and medical costs associated with narcolepsy.

This study provides an up-to-date review of the clinical spectrum of narcolepsy initiatives were suggested as the proposed solution. This survey concluded that there are substantial gaps in understanding narcolepsy been highlighted as:

Papers of particular interest, published within the annual period of review, have

According to the study, the medical costs associated with narcolepsy are substantial, and there are significant gaps in understanding the condition. The study highlights the need for further research and initiatives to improve the clinical spectrum of narcolepsy.

A practical guide to the therapy of narcolepsy and hypersomnia syndromes. 2013:797–773.

A comprehensive review of the management of hypersomnia of central origin.

The study suggests a new pathophysiological pathway for EDS and possible

This article provides a comprehensive historical review regarding narcolepsy.


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