Update on hypersomnias of central origin

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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.

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 γ-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.

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.

Keywords
behaviourally induced insufficient sleep syndrome, cataplexy, idiopathic hypersomnia, Kleine–Levin syndrome, narcolepsy

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 [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 [3].

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

Hypersomnias of central origin are classified as follows [4▪▪]:

(1) narcolepsy type 1 [narcolepsy with cataplexy or deficient 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.

NARCOLEPSY

Narcolepsy represents the classic hypersomnia of central origin, and is the best understood of these conditions.

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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.

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 and find these brief naps refreshing [5▪].

Hypnogogic hallucinations, typically visual but sometimes auditory or sensory, affect 30–60% of patients. These may occur at sleep onset or sleep offset, and can be bizarre and frightening. Hallucinations may accompany sleep paralysis, which is especially frightening and both more frequently occur at sleep onset. This can result in experiences of being physically or sexually assaulted and shortness of breath, causing significant anxieties surrounding sleep. Sleep paralysis, which affects 25–50%, can be partial or complete and occurs in full consciousness.

The final feature of the classical tetrad is cataplexy, which usually develops within 3–5 years of onset of EDS (it can occur up to 45 years later), but rarely precedes it [6]. Cataplexy is defined as the transient and sudden loss of muscle tone in full consciousness, usually precipitated by strong emotion or occasionally spontaneously; it occurs in 60–70% of patients. It may be complete, affecting all muscles – apart from the diaphragm and the extraocular muscles – or may be segmental, affecting only the limbs, face or muscles affecting speech. Cataplexy typically lasts seconds or minutes, but may be more prolonged, especially following sudden withdrawal of anticataplectic agents – 'status cataplecticus'. Neurophysiological studies suggest that cataplexy reflects an exaggerated physiological mechanism [7].

Other features of narcolepsy include rapid eye movement (REM) sleep behaviour disorder (RBD); in the elderly, RBD is frequently a harbinger of idiopathic Parkinson's disease or of dementia with Lewy bodies, whereas in the young it is often associated with narcolepsy [8–10]. Patients also may have an increased frequency of periodic limb movement disorder and obstructive sleep apnea affecting sleep quality [11,12].

Narcolepsy affects approximately one in 3000 people. The age of onset ranges from early childhood to the fifth decade, but there is a bimodal distribution, with peaks of onset between 15 and 36 years of age [13–15].

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].

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:

(1) narcolepsy type 1
   (a) The patient has daily periods of irrepressible 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 SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs 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 irrepressible 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 SOREMPs on an MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs 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 hypersomnolence 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 (NREM1) 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 anticataplectic 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 anticataplectic 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 ($GABA_B$) 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 1. Common drugs for excessive daytime sleepiness and cataplexy

	Duration of action	Typical starting dose	Usual maintenance dose	Frequent side-effects	Serious side-effects	Cautions	Comments
Drugs for excessive daytime sleepiness							
Modafinil	8–16 h	100 mg o.d.	100–400 mg/day in one or two doses, with latest dose before 2 p.m.	Headache, nausea, gastrointestinal upset, anxiety, insomnia, palpitations, aggression	Drug rash including Stevens–Johnson Syndrome, anaphylactoid reactions, hypertension	Avoid in patients with left ventricular hypertrophy or mitral valve prolapse. Potential interaction with hormonal contraceptives	Low potential for abuse. Can be used in conjunction with amphetamines
Methylphenidate	3–4 h normal release preparation 6–10 h sustained release preparation	5 mg b.i.d. 10–18 mg once-daily, depending on brand	10–60 mg/day in 2–3 divided doses 100–108 mg once-daily, depending on brand	Anxiety, tremor, palpitations, weight loss, gastrointestinal upset, dry mouth	Hypersensitivity reactions, depression, hypomania, psychosis, hypertension, reduced seizure threshold, arrhythmias	Avoid in severe psychiatric disease, cardiovascular disease, cerebrovascular disease and phaeochromocytoma	Potential for abuse. Mild anticataplectic activity
Dexamphetamine	6–10 h	5–10 mg daily in one or two doses	10–60 mg per day in two doses	Dizziness, anxiety, flushing, dry mouth, headache, blurred vision, gastrointestinal upset, weight loss	Hypersensitivity reactions, seizures, arrhythmias, paranoia, psychosis, withdrawal effects, cerebral vasculopathy	Contraindicated in severe hypertension, structural cardiac abnormalities, advanced atherosclerosis, previous substance abuse. Contraindicated with MAOIs	Significant potential for abuse. Mild anticataplectic activity
Drugs for cataplexy							
Clomipramine		10 mg nocte	10–75 mg nocte	Antimuscarinic side-effects, postural hypotension, confusion, sedation, agitation, weight gain	Arrhythmias, heart block, suicidal behaviour, myoclonus, allergic alveolitis		May be helpful with prominent nighttime insomnia. Can exacerbate PLMD

(*Continued*)

Table 1 (*Continued*)

	Duration of action	Typical starting dose	Usual maintenance dose	Frequent side-effects	Serious side-effects	Cautions	Comments
Venlafaxine (sustained release)		37.5 mg o.m.	75–225 mg daily	Headache, nausea, sexual dysfunction, insomnia, dizziness, sweating	Risk of suicide, cardiac arrhythmias, hypersensitivity reactions, extrapyramidal reactions, neuroleptic malignant syndrome	Contraindicated with high risk of arrhythmias, uncontrolled hypertension; Withdrawal can be problematic; Caution in heart disease, history of epilepsy, history of mania, bleeding disorders; Can have a mild stimulant effect	
Sodium oxybate		2.25 g twice nightly	3–4.5 g twice nightly	Nausea, gastrointestinal upset, hypertension, peripheral oedema, confusion, sleep walking, sedation, nocturnal enuresis	Psychosis, depression, amnesia, suicidal ideation, seizures	Avoid in patients with psychiatric history and uncontrolled sleep apnea	Titration regimen involves assessment and increase in dose every 2 weeks. Has potential to be used as a 'date-rape' drug. Effective for EDS in N+C

EDS, excessive daytime sleepiness; o.d., every day/once-daily; o.m., every morning; PLMD, periodic limb movement disorder; MAOIs, monoamine oxidase inhibitors. Reproduced with permission from [4▪▪].

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 ($GABA_A$) 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 form 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 $GABA_A$ 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 irrepressible 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 $GABA_A$ 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.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Black J, Reaven NL, Funk SE, *et al.* The Burden of Narcolepsy Disease ■ (BOND) study: health-care utilization and cost findings. Sleep Med 2014; 15:522–529.

This is the first study that demonstrates the significantly higher rates of healthcare utilization and medical costs associated with narcolepsy.

2. Rosenberg R, Kim AY. The AWAKEN survey: knowledge of narcolepsy ■ among physicians and the general population. Postgrad Med 2014; 126:78–86.

This survey concluded that there are substantial gaps in understanding narcolepsy and its symptoms even among sleep medicine specialists, and educational initiatives were suggested as the proposed solution.

3. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004; 5:37–41.
4. American Academy of Sleep Medicine. International classification of sleep ■■ disorders. 3rd ed. IL: American Academy of Sleep Medicine D; 2014.

An update on the classification of sleep disorders.

5. Leschziner G. Narcolepsy: a clinical review. Pract Neurol 2014. doi: 10.1136/ ■ practneurol-2014-000837.

This study provides an up-to-date review of the clinical spectrum of narcolepsy along with the useful advice for clinical practice.

6. Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy: a reappraisal. J Sleep Res 2004; 13:395–406.
7. Lammers GJ, Overeem S, Tijssen MA, van Dijk JG. Effects of startle and laughter in cataplectic subjects: a neurophysiological study between attacks. Clin Neurophysiol 2000; 111:1276–1281.
8. Nightingale S, Orgill JC, Ebrahim IO, *et al.* The association between narcolepsy and REM behavior disorder (RBD). Sleep Med 2005; 6:253–258.
9. Pisko J, Pastorek L, Buskova J, *et al.* Nightmares in narcolepsy: underinvestigated symptom? Sleep Med 2014; 15:967–972.
10. Dauvilliers Y, Jennum P, Plazzi G. Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia in narcolepsy. Sleep Med 2013; 14:775–781.
11. Sonka K, Kemlink D, Buskova J, *et al.* Obesity accompanies narcolepsy with cataplexy but not narcolepsy without cataplexy. Neuro Endocrinol Lett 2010; 31:631–634.
12. Frauscher B, Ehrmann L, Mitterling T, *et al.* Delayed diagnosis, range of severity, and multiple sleep comorbidities: a clinical and polysomnographic analysis of 100 patients of the Innsbruck Narcolepsy Cohort. J Clin Sleep Med 2013; 9:805–812.
13. Dauvilliers Y, Montplaisir J, Molinari N, *et al.* Age at onset of narcolepsy in two large populations of patients in France and Quebec. Neurology 2001; 57:2029–2033.
14. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. Sleep Med 2014; 15:502–507.
15. Krishnamurthy VB, Nallamothu V, Singareddy R. An interesting case of late age at onset of narcolepsy with cataplexy. J Clin Sleep Med 2014; 10:203–205.
16. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998; 50:S16–S22.
17. Tafti M, Hor H, Dauvilliers Y, *et al.* DQB1 locus alone explains most of the risk ■ and protection in narcolepsy with cataplexy in Europe. Sleep 2014; 37:19–25.

This study is one of the largest in scale to be conducted, and describes the association between HLA-DQB1*06:02 and primary and secondary narcolepsy.

18. Barker CI, Snape MD. Pandemic influenza A H1N1 vaccines and narcolepsy: vaccine safety surveillance in action. Lancet Infect Dis 2014; 14:227–238.
19. De la Herran-Arita AK, Kornum BR, Mahlios J, *et al.* $CD4^+$ T cell autoimmunity to hypocretin/orexin and cross-reactivity to a 2009 H1N1 influenza A epitope in narcolepsy. Sci Transl Med 2013; 5:216ra176.
20. Thebault S, Vincent A, Gringras P. Narcolepsy. H1N1 vaccination: a link? Curr ■ Opin Pulm Med 2013; 19:587–593.

This review summarizes all the current observations regarding the association between the 2009 H1N1 vaccination and narcolepsy.

21. Aran A, Lin L, Nevsimalova S, *et al.* Elevated antistreptococcal antibodies in patients with recent narcolepsy onset. Sleep 2009; 32:979–983.
22. Wu H, Zhuang J, Stone WS, *et al.* Symptoms and occurrences of narcolepsy: a retrospective study of 162 patients during a 10-year period in Eastern China. Sleep Med 2014; 15:607–613.
23. Mignot EJ. History of narcolepsy at Stanford University. Immunol Res 2014; ■ 58:315–339.

This article provides a comprehensive historical review regarding narcolepsy.

24. Van der Most R, Van Mechelen M, Destexhe E, *et al.* Narcolepsy and A(H1N1)pdm09 vaccination: shaping the research on the observed signal. Hum Vaccin Immunother 2013; 10:572–576.
25. Heier MS, Gautvik KM, Wannag E, *et al.* Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1 influenza A. Sleep Med 2013; 14:867–871.
26. Thannickal TC, Moore RY, Nienhuis R, *et al.* Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000; 27:469–474.
27. Tabuchi S, Tsunematsu T, Black SW, *et al.* Conditional ablation of orexin/ hypocretin neurons: a new mouse model for the study of narcolepsy and orexin system function. J Neurosci 2014; 34:6495–6509.
28. Singh AK, Mahlios J, Mignot E. Genetic association, seasonal infections and autoimmune basis of narcolepsy. J Autoimmun 2013; 43:26–31.
29. De la Herran-Arita AK, Garcia-Garcia F. Narcolepsy as an immune-mediated disease. Sleep Disord 2014; 2014:792687.
30. Mahlios J, De la Herran-Arita AK, Mignot E. The autoimmune basis of narcolepsy. Curr Opin Neurobiol 2013; 23:767–773.
31. Drakatos P, Kosky CA, Higgins SE, *et al.* First rapid eye movement sleep ■ periods and sleep-onset rapid eye movement periods in sleep-stage sequencing of hypersomnias. Sleep Med 2013; 14:897–901.

Stage sequence of first rapid eye movement sleep periods and SOREMPs as an additional tool in the diagnosis of narcolepsy.

32. Drakatos P, Suri A, Higgins SE, *et al.* Sleep stage sequence analysis of sleep onset REM periods in the hypersomnias. J Neurol Neurosurg Psychiatry 2013; 84:223–227.
33. Philip P, Chaufton C, Taillard J, *et al.* Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep 2014; 37:483–487.
34. Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia ■ syndromes. Neurotherapeutics 2012; 9:739–752.

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

35. Nittur N, Konofal E, Dauvilliers Y, *et al.* Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. Sleep Med 2013; 14:30–36.
36. Boscolo-Berto R, Viel G, Montagnese S, *et al.* Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012; 16:431–443.
37. Valko PO, Khatami R, Baumann CR, Bassetti CL. No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy. J Neurol 2008; 255:1900–1903.
38. Trotti LM, Saini P, Freeman AA, *et al.* Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: clinical experience. J Psychopharmacol 2013; 28:697–702.
39. Mieda M, Sakurai T. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders. Rationale for development and current status. CNS Drugs 2013; 27:83–90.
40. Weinhold SL, Seeck-Hirschner M, Nowak A, *et al.* The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. Behav Brain Res 2014; 262:8–13.
41. De la Herran-Arita AK, Garcia-Garcia F. Current and emerging options for the drug treatment of narcolepsy. Drugs 2013; 73:1771–1781.
42. Inocente C, Arnulf I, Bastuji H, *et al.* Pitolisant, an inverse agonist of the histamine H3 receptor: an alternative stimulant for narcolepsy–cataplexy in teenagers with refractory sleepiness. Clin Neuropharmacol 2012; 35:55–60.
43. Billiard M, Dauvilliers Y. Idiopathic hypersomnia. Sleep Med Rev 2001; 5:349–358.
44. Billiard M, Besset A. Idiopathic hypersomnia. Sleep, physiology, investigations and medicine. New York: Kluwer Academic/Plenum Publishers; 2003; 429–435.
45. Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. Neurology 1996; 46:393–401.
46. Faull KF, Thiemann S, King RJ, Guilleminault C. Monoamine interactions in narcolepsy and hypersomnia: a preliminary report. Sleep 1986; 9:246–249.
47. Malhotra S, Kushida CA. Primary hypersomnias of central origin. Continuum (Minneap Minn) 2013; 19:67–85.
48. Rye DB, Bliwise DL, Parker K, *et al.* Modulation of vigilance in the primary ■■ hypersomnias by endogenous enhancement of GABAA receptors. Sci Transl Med 2012; 4:161ra151.

This study suggests a new pathophysiological pathway for EDS and possible benefits from a BZD antagonist – flumazenil, administration.

49. Trotti LM, Staab BA, Rye DB. Test–retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. J Clin Sleep Med 2013; 9:789–795.
50. Kelty E, Martyn V, O'Neil G, Hulse G. Use of subcutaneous flumazenil preparations for the treatment of idiopathic hypersomnia: a case report. J Psychopharmacol 2014; 28:703–706.
51. Arnulf I, Rico TJ, Mignot E. Diagnosis disease course, and management of patients with Kleine–Levin syndrome. Lancet Neurol 2012; 11:918–928.

52. Billiard M, Podesta C. Recurrent hypersomnia following traumatic brain injury. Sleep Med 2013; 14:462–465.
53. Engstrom M, Karlsson T, Landtblom AM. Reduced thalamic and pontine connectivity in Kleine–Levin syndrome. Front Neurol 2014; 5:42.
54. Dauvilliers Y, Bayard S, Lopez R, *et al.* Widespread hypermetabolism in symptomatic and asymptomatic episodes in Kleine–Levin syndrome. PLoS One 2014; 9:e93813.
55. Miglis MG, Guilleminault C. Kleine–Levin syndrome: a review. Nat Sci Sleep ■ 2014; 6:19–26.
An up-to-date review on the Kleine–Levin syndrome.
56. Billiard M, Jaussent I, Dauvilliers Y, Besset A. Recurrent hypersomnia: a review of 339 cases. Sleep Med Rev 2011; 15:247–257.
57. Pizza F, Peltola H, Sarkanen T, *et al.* Childhood narcolepsy with cataplexy: comparison between post-H1N1 vaccination and sporadic cases. Sleep Med 2014; 15:262–265.