Sleep and Sleep Disorders 1

Understanding and approaching excessive daytime sleepiness

Laura Pérez-Carbonell, Emmanuel Mignot, Guy Leschziner, Yves Dauvilliers

Excessive daytime sleepiness (EDS) is a public health issue. However, it remains largely undervalued, scarcely diagnosed, and poorly supported. Variations in the definition of EDS and limitations in clinical assessment lead to difficulties in its epidemiological study, but the relevance of this symptom from a socioeconomic perspective is inarguable. EDS might be a consequence of several behavioural issues leading to insufficient or disrupted sleep, as well as a consequence of sleep disorders including sleep apnoea syndrome, circadian disorders, central hypersomnolence disorders (narcolepsy and idiopathic hypersomnia), other medical or psychiatric conditions, or medications. Furthermore, EDS can have implications for health as it is thought to act as a risk factor for other conditions, such as cardiovascular and neurodegenerative disorders. Because of the heterogeneous causes of EDS and the complexity of its pathophysiology, management will largely depend on the cause, with the final aim of making treatment specific to the individual using precision medicine and personalised medicine.

Lancet 2022; 400: 1033–46

Published Online September 14, 2022 https://doi.org/10.1016/S0140-6736(22)01018-2

This is the first in a Series of four papers about sleep and sleep disorders (paper 4 appears in *The Lancet Neurology*). All papers in the Series are available at www.thelancet.com/series/sleep-disorders

Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK (L Pérez-Carbonell MD, Prof G Leschziner MD PhD); **Center for Narcolepsy, Stanford University, Palo Alto, CA, USA** (Prof E Mignot MD PhD); **Basic and Clinical Neurosciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK** (G Leschziner); **Centre National de Référence Narcolepsie Hypersomnies, Unité des Troubles du Sommeil, Département de Neurologie, Hôpital Gui-de-Chauliac, Inserm INM, Université Montpellier, Montpellier, France** (Prof Y Dauvilliers MD PhD)

Correspondence to: Dr Laura Pérez-Carbonell, Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London SE1 1UL, UK **laura.perezcarbonell@gstt.nhs.uk**

Introduction

Sleep is important for human health and wellbeing. Sleeping well at night and feeling awake in the day are relevant to quality of life, adequate social functioning, and physical and psychological health. Therefore, the clinical approach to a patient complaining of being sleepy is important.

The urge to sleep during the day when the intention of an individual is to remain alert is one of the most frequent complaints reported in sleep medicine consultations. The *International Classification of Sleep Disorders* (3rd edition)[1] defines excessive daytime sleepiness (EDS) as the inability to stay awake and alert during major waking episodes (the longest period in 24 h that a person would typically be awake), resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. However, the clinical presentation of EDS can vary between patients, including a continuous state of persistent somnolence, an abrupt overwhelming sleepiness arising without warning that results in sleep attacks, or unintended naps commonly associated with monotonous activities that are not as sudden or unanticipated as sleep attacks. Alternative terms, such as hypersomnolence, hypersomnia, fatigue, or apathy, are often misused in clinical practice, scientific literature, and classifications of sleep disorders when discussing EDS (panel 1).[4–7] These terms are incorrectly used interchangeably as semantic distinctions are not given enough consideration.[3,8] As previously reported,[3] the concept of hypersomnolence should be defined as EDS, excessive quantity of sleep (eg, hypersomnia, defined as ≥10 h asleep during 24 h, with ≥9 h of sleep at night), or sleep inertia (eg, an alteration in vigilance after waking up).[3] This Series paper will focus specifically on EDS.

The aim of this Series paper is to discuss the prevalence of EDS and its different characteristics, to give an overview of its assessment, causes, pathophysiology, and clinical relevance as a possible risk factor for some conditions, and to summarise its management options.

The second and third papers in this Series are published in *The Lancet* and discuss insomnia[9] and disorders of the timing of sleep,[10] and the fourth paper is published in *The Lancet Neurology* and discusses an evolutionary perspective of sleep function.[11]

Prevalence and risk factors of EDS

The reported prevalence of EDS varies substantially (2·5–33%),[12–14] and changes depending on the population studied and the definition and assessment of EDS used.[15] When EDS is evaluated with a self-report assessment tool, such as the Epworth Sleepiness Scale, its prevalence in the general population continues to show substantial variation (8·5–22%).[12] Demographic and cultural factors (eg, age of respondents, caffeine consumption, and other lifestyle factors), study design differences, and varying scale performances can account for this variation. The incidence of EDS reported in longitudinal studies also

Search strategy and selection criteria

We searched references in PubMed published between Jan 1, 1990, and March 1, 2022 using the terms "sleepiness", "hypersomnia", "hypersomnolence", "somnolence", "excessive somnolence", and "excessive daytime sleepiness".
We examined articles published in French and English. We also searched the reference lists of retrieved articles. We then selected the most relevant references, paying particular attention to studies within the past 20 years (although we retained some older studies for their importance) and studies with large samples and control groups. The final reference list was agreed upon by author consensus based on originality, impact, and relevance to the aims of our Series paper.

Panel 1: **Glossary of terms used when approaching a patient with EDS**

Excessive daytime sleepiness (EDS): an inability to stay awake or alert during major waking episodes resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep.[2]

Excessive need for sleep: a need for an excessive quantity of sleep during a 24 h period (≥10 h of sleep needed during 24 h with night-time providing ≥9 h of sleep duration) associated with impairment and distress primarily related to deteriorated quality of daytime wakefulness, which cannot be fully resolved by increasing the amount of sleep.[3]

Hypersomnolence: excessive daytime sleepiness, excessive quantity of sleep (eg, hypersomnia, defined as ≥10 h asleep during 24 h, with ≥9 h of sleep at night), or sleep inertia (ie, impairment in vigilance after waking up).[3]

Hypersomnia: increased quantity of sleep during a 24 h period[4] or objectively assessed excessive need for sleep (an objective assessment of an excessive quantity of sleep requires ≥10 h of sleep duration during 24 h, with night-time providing ≥9 h of sleep duration).[3]

Clinophilia: prolonged periods of time spent in bed with no objective evidence for increased duration of sleep.[3]

Fatigue: physical or mental exhaustion with difficulties initiating or sustaining voluntary activities. Difficulties and exhaustion are not substantially improved by increased rest or sleep.[3,5]

Apathy: reduced self-generated voluntary or purposeful behaviours.[6]

See Online for appendix

Sleep inertia: major difficulties waking up in the morning or after a nap with frequent re-entries into sleep, reduced vigilance, and impaired cognitive performance lasting from a few minutes to hours. So-called sleep drunkenness is its extreme manifestation,[3] alongside confusion and clumsiness.

shows variability (5–28% after 5 years of follow-up[12,15,16] and 8% after 7·5–10 years of follow-up).[13,17] Additionally, fluctuation of the course of EDS over time has been described, with 15–44% of participants reporting persistent EDS after a 5-year follow-up.[12,16]

Data are scarce on factors associated with EDS onset and its natural history. Depression,[12,13,16] insomnia,[12,13] chronic pain,[12] smoking,[12,13] and consuming a small amount of coffee are independent risk factors for the development of EDS in longitudinal studies.[12] Being male, poor sleep quality, and moderate-severe obstructive sleep apnoea have also been identified as independent predictors of EDS.[16] Diabetes was associated with persistent EDS in a longitudinal study with a 5-year follow-up,[12] whereas EDS remission was associated with having healthy bodyweight, hypertension, and reduction of depression and insomnia symptoms.[14] Obesity was identified as a major risk factor for both incident EDS and persistent EDS during a 7·5-year follow-up.[17] In another population-based cohort,[16] a reduction in sleep duration over time was associated with an increased risk of persistent EDS, whereas discontinuation of drugs influencing sleep reduced this risk.

Studies focusing on the prevalence of EDS in children and adolescents estimate that 4–84% of all included children and adolescents have EDS, with a higher prevalence in adolescence than in childhood. There is an association between EDS and emotional difficulties, behavioural difficulties, poor mental health, and being female at mid-puberty stages.[18–21] In adults, children, and adolescents, insufficient sleep is commonly an underlying cause of EDS.[20,21]

Excessive quantity of sleep and sleep inertia are other sleep symptoms frequently associated with EDS. The frequency of an excessive duration of night-time sleep (defined as ≥9 h of sleep in 1 night) is 8·4% in the general population, with a higher prevalence in women (9·2%) than in men (7·6%), and with a large age effect (decreasing until age 65 years and increasing thereafter).[22,23] Excessive night-time sleep was associated with substantial daytime consequences, such as impaired functioning or distress due to excessive sleep, in 1·6% of a study population.[22,23] Because there is no standard definition of sleep inertia there is no robust data on its prevalence (panel 1). However, a large study reported that sleep inertia was found in 1·2% of the general population.[22]

Clinical and neurophysiological assessment of EDS

The assessment of EDS requires a rigorous clinical approach (appendix p 2) completed by use of self-report questionnaires and neurophysiological measures, depending on the clinical context. Several types of EDS might be seen within the same condition and be reported by a single patient. Although clinical distinctions between different EDS presentations are not routinely considered when assessing sleepiness, these distinctions are important to discuss with patients as they have diverse effects on the lives of patients and their ability to function during daytime. Onset of EDS, progression over time, triggering factors, degree of sleepiness (eg, in which situations the patient has EDS), impairment of daily activities, duration and characteristics of naps, and presence of sleep attacks should be evaluated.

After doing a clinical interview (appendix p 2) there are different tests to measure EDS, but results do not always correlate. Self-report measures and objective assessments answer different questions depending on the nature and requirements of the given test (panel 2). A neurophysiological assessment of EDS might be needed to objectively quantify severity. This assessment is often done with the multiple sleep latency test (MSLT), which measures the propensity of an individual to fall asleep under controlled conditions during the day. By

Panel 2: **Self-report and objective assessment of excessive daytime sleepiness (EDS) and wakefulness**

Self-report assessment (eg, questionnaires or scales)
Several self-report measurements (eg, the 7-point Stanford Sleepiness Scale, the 9-point Karolinska Sleepiness Scale, or visual analogue scales) have been developed to measure sleepiness at a given time. Scores on these scales measure the patient's perception of their degree of sleepiness.

The most frequently used scale is the Epworth Sleepiness Scale. This scale is a simple self-administered questionnaire that asks the patient to evaluate, during the preceding month, how likely they were on a scale of 0 to 3 to doze or go to sleep in eight different situations that are regularly encountered in daily life. These scenarios range from "lying down to rest in the afternoon when circumstances permit" to "sitting and talking to someone".[24]

Objective assessment (eg, neurophysiological)
Multiple sleep latency test (MSLT)
- It is the most widely used objective test in clinical practice and is often considered to be the gold standard for the objective diagnosis of EDS
- The assumption of the MSLT is that a patient falls asleep faster when they are sleepier
- The third edition of the *International Classification of Sleep Disorders* uses the MSLT mean sleep latency to establish a diagnosis of narcolepsy or idiopathic hypersomnia
- Patients not complaining of EDS have a mean sleep latency of more than 12 min and patients with objective EDS have a mean sleep latency of less than or equal to 8 min
- Results are sometimes difficult to interpret due to interindividual variability and a wide variation of test results in the general population
- Some patients without a complaint of EDS but who fall asleep quickly can present mean sleep latencies less than 8 min on the MSLT; conversely, some patients with disorders of hypersomnolence can have mean sleep latencies of more than 12 min
- Important variations in the MSLT results can occur based on the time of day at which the tests are taken, stress linked to admission to hospital in a sleep unit, the importance of the results for diagnosis, the effects of sleep deprivation, the use of sedatives or stimulants, and patient age; the MSLT provides a precise measurement of objective EDS in an experimental situation that is different from the daily life of a patient

MSLT protocol
- The patient is lying down on a bed and is instructed to "please lie quietly, keep your eyes closed and try to fall asleep"[25]
- There is a fixed protocol for the MSLT during five sessions (0900 h, 1100 h, 1300 h, 1500 h, and 1700 h)
- Each session is interrupted after 20 min if the patient has not fallen asleep or 15 min after the patient falls asleep
- If the patient falls asleep, they are allowed to sleep for 15 min to assess sleep onset rapid eye movement (REM) period (SOREMP)
- Wakefulness-promoting and REM sleep-suppressing medications should be stopped 2 weeks (or 5 half-lives) before the MSLT
- The main outcome is mean sleep latency corresponding to the average time the patient takes to fall asleep in the five sessions

Maintenance of wakefulness test (MWT)
- The assumption of the test is that a patient falls asleep faster than an individual who is not sleepy
- Several thresholds have been proposed to consider mean sleep latency as pathological ranging from 19 min (the most widely accepted threshold) to 33 min (threshold to minimise accident risk) or even 40 min (not falling asleep, the most conservative threshold)
- The MWT is generally used in clinical practice to measure the effectiveness of stimulant treatments and sometimes to find out whether a professional driver with EDS can return to driving

MWT protocol
- The patient is seated in a chair in low-light conditions with the instruction to sit still and remain awake for as long as possible
- The MWT consists of four sessions with a fixed protocol (1000 h, 1200 h, 1400 h, and 1600 h)
- Each session is interrupted after 40 min if the patient has not fallen asleep or after unequivocal sleep onset
- Patients are not allowed to use extraordinary measures to stay awake (eg, reading, singing, or pinching themselves)
- Drug screening is performed in some centres before the MWT to verify the absence of sedating or stimulant drugs

Extended polysomnography
- Especially useful when idiopathic hypersomnia is suspected
- The procedures concerning time spent in bed, authorised activities (eg, television, computer, physical activity), ambient light, and stimulants taken (eg, coffee or tobacco) during the recording should be standardised
- Extended polysomnography recording should be 24 h (or more if possible) after polysomnography and the MSLT; the MSLT should be stopped as soon as the patient lapses into sleep to respect homoeostasis in strict bedrest without environmental stimulants

contrast, the maintenance of wakefulness test (MWT), another neurophysiological test, measures the capacity of an individual to remain awake during the day. The MWT is indicated as one of the criteria for measuring fitness to drive in people treated for a disorder of hypersomnolence (panel 2).[26]

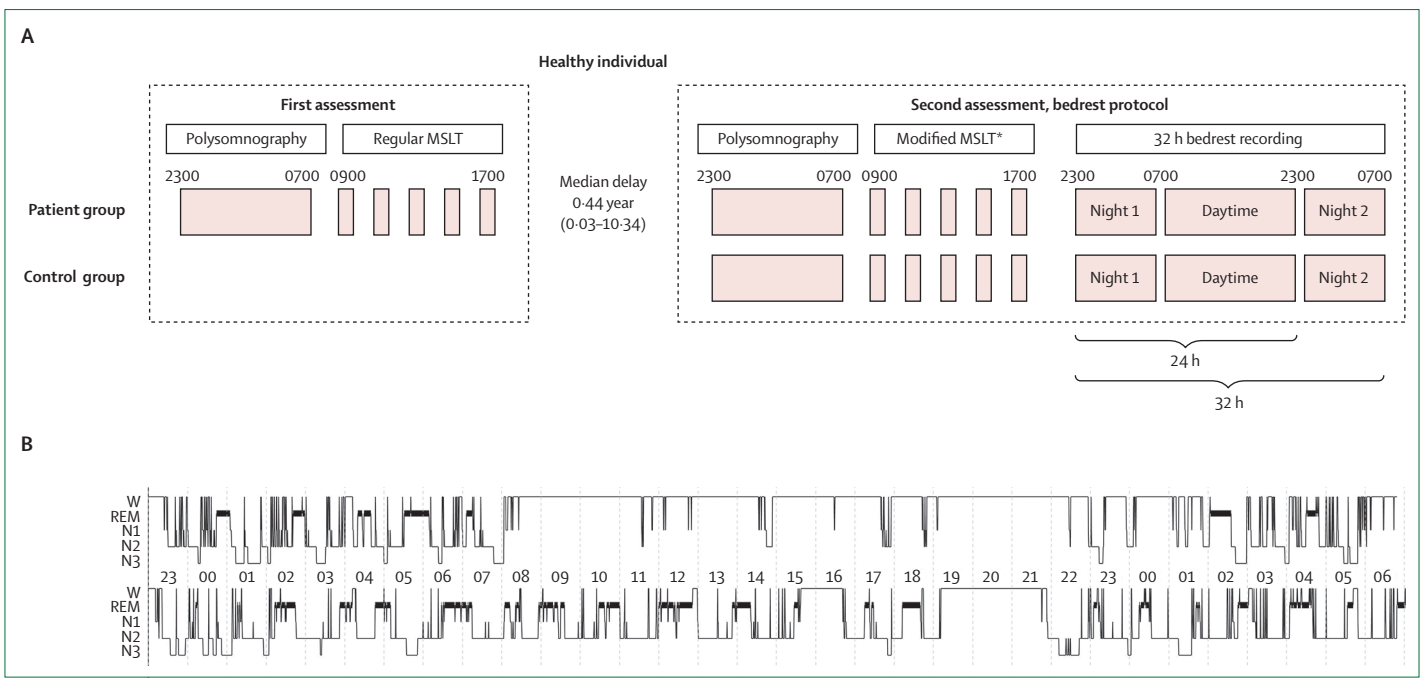

Figure 1: **Extended sleep duration on a controlled 32 h bed-rest protocol**

(A) The suggested protocol for patients with suspected idiopathic hypersomnia involves a polysomnography recording of 8 h from 2300 to 0700, followed by MSLT, then 32 h continuous polysomnography recording including 2 nights and 1 day under standardised conditions. (B) Hypnogram of a control individual and a patient with idiopathic hypersomnia with extended nocturnal and daytime sleep. MSLT=multiple sleep latency test. *Modified MSLT is defined as five nap opportunities every 2 h between 0900 and 1700, in which patients are awakened after 1 min of sleep. Reproduced from Evangelista and colleagues,[29] by permission of John Wiley and Sons.

Despite normative values for MSLT and MWT, interpretation of results of these tests is not absolute and results can correlate poorly with self-report measures (eg, Epworth Sleepiness Scale).[27,28] Therefore, the interpretation of the results of these tests should always be done in the clinical context, with additional assessments sometimes required depending on the particular clinical suspicion. Respiratory polygraphy or home respiratory sleep testing should be done when obstructive sleep apnoea is suspected. When insufficient sleep or a circadian sleep–wake disorder is suspected as the potential cause of EDS, encouraging the patient to keep a sleep diary and doing actigraphy (a non-invasive method monitoring the rest and activity cycles of an individual that provides an estimation of the total sleep time) can aid diagnosis. Polysomnography might be needed if an underlying sleep-disrupting pathology is thought to be the cause of EDS, and should be done before the MSLT. To confirm excessively long nocturnal sleep, recording of continuous ad libitum sleep during a period of at least 24 h might be needed (panel 2, figure 1), especially in the context of suspected idiopathic hypersomnia.[30] Actigraphy can also be useful in assessing extended nocturnal sleep in patients with hypersomnolence in ambulatory care during long periods of time under natural conditions. However, despite being well accepted and less expensive than polysomnography, actigraphy can overestimate sleep at night and underestimate wakefulness during the day.[31] Finally, sleep inertia, another important hypersomnolence symptom, can be quantified by the psychomotor vigilance task (PVT). PVT can be useful for the characterisation, management, and follow-up of sleep inertia in patients with idiopathic hypersomnia.[32]

Causes of EDS

Commonly, EDS is a consequence of sleep deprivation, poor night-time sleep, other sleep disorders such as obstructive sleep apnoea, and circadian rhythm disorders. EDS might be the core symptom of central disorders of hypersomnolence (eg, narcolepsy and idiopathic hypersomnia). EDS can also relate to medical conditions (eg, neurological, endocrinological, renal, liver, or respiratory diseases), psychiatric conditions (eg, depression), or arise as an iatrogenic effect of medications. It is not unusual to see patients with multiple causes of EDS.

Insufficient sleep syndrome, poor night-time sleep, and sleep-disordered breathing

Insufficient sleep syndrome is a public health problem, often the primary cause of EDS (20–30% of adults), that occurs as sleep time is insufficient due to reduced time in bed. People aged 18–60 years should sleep about 7 h per night on a regular basis for optimal sleep health.[33] A detailed history of sleep pattern showing short sleep duration (eg, <6 h of sleep per day) with large differences

between sleep duration on weekend nights and holidays compared with weekday nights is suggestive of insufficient sleep.

Sleep-disordered breathing is the most common condition, apart from chronic sleep restriction, likely to be the cause of EDS. Sleep-disordered breathing is estimated to affect up to one in seven people worldwide.[34] Obstructive sleep apnoea is characterised by snoring, gasping, and oxygen desaturations, often with disturbed and unrefreshing night-time sleep. EDS, fatigue, impaired vigilance, and cognitive dysfunction are common daytime complaints of obstructive sleep apnoea.[35] Although sleep apnoea typically occurs in overweight men, with prevalence increasing as age increases, sleep apnoea can also occur in children (notably with tonsillar hypertrophy), women, and individuals with an anatomically small upper airway (eg, micrognathia). The reason why only about half of patients with sleep apnoea complain of EDS is poorly understood. Furthermore, some patients (approximately 6%) report persistent EDS despite adequate amounts of sleep and optimal treatment of their obstructive sleep apnoea.[36,37] In most cases of obstructive sleep apnoea, mean sleep latencies were more than 8 min on the MSLT. Residual symptoms of sleep apnoea can also include fatigue and mild depressive symptoms resulting in impaired quality of life, suggesting a true syndrome that is resistant to continuous positive airway pressure (CPAP) therapy that does not appear to be associated with extended hypoxic exposure. Moreover, EDS might occur in obesity hypoventilation syndrome, which involves metabolic and circadian dysregulations.[38]

Fragmented sleep and sleep restriction can also be related to restless legs syndrome and periodic limb movement disorder, which typically cause hyperarousal but can also manifest with EDS.[39]

Circadian disturbances

EDS can also be a consequence of circadian rhythm disorders, which can be behaviourally induced (eg, via jet lag or shift work). Circadian rhythm sleep–wake disorders occur when the internal clock of an individual, which informs them when it is time to sleep or to wake, is out of synchrony with the environment. The delayed sleep–wake phase disorder occurs when a sleep pattern is delayed by 2 h or more from a conventional sleep pattern, causing an individual to go to sleep later and wake up later than is considered conventional. Advanced sleep–wake phase disorder is defined by sleep–wake schedules that occur earlier than desired (eg, before socially acceptable times), alongside evening sleepiness and early morning awakening. Delayed sleep–wake phase disorder and advanced sleep–wake phase disorder can result in EDS, difficulty initiating and maintaining sleep, or both. These disorders are caused by alteration of the circadian timekeeping system, the entrainment mechanisms of the system, or a misalignment of the endogenous circadian rhythm and the external environment.

Central hypersomnolence disorders

Narcolepsy type 1 (NT1) affects approximately 0·03% of the population worldwide and begins most often in childhood or adolescence.[40] NT1 can have a very abrupt onset, notably in children, and is associated with weight gain. It occurs as a result of the selective loss of approximately 60 000–80 000 neurons that secrete the wake-promoting neuropeptide orexin (also known as hypocretin).[41] The disorder is strongly associated with *HLA-DQB1*06:02*, and the loss of the neurons is presumed to be immune-based.[42] EDS is mandatory for a diagnosis of NT1, is often severe, and is characterised by short, refreshing naps associated with having dreams, sometimes with true sleep attacks. The pathognomonic symptom is cataplexy, which can be characterised by sudden generalised muscle weakness with complete atonia resulting in total collapse. More commonly, cataplexy presents with short-lasting, abrupt, and partial muscle weakness affecting facial and neck muscles, resulting in head drop, jaw tremor, or difficulties with smiling. It can also affect upper or lower limbs through dropping objects or weakness of the knees. Cataplexy episodes are triggered by strong and often positive emotions, such as laughing, being surprised, meeting a friend, or telling a joke. Narcolepsy is not typically associated with extended sleep duration, and sleep at night is often disturbed with several bouts of wake and sleep.[43] Sleep-related hallucinations, sleep paralysis, and vivid dreams might also be reported.[40]

NT1 is a clearly delineated disease entity (panel 3), with cerebrospinal fluid hypocretin deficiency as a diagnostic test[44] and cataplexy. However, two other key central hypersomnolence disorders, narcolepsy type 2 (NT2) and idiopathic hypersomnia, share less robust and specific criteria than NT1 (panel 3). Although NT2 and idiopathic hypersomnia are differentiated by sleep specialists, the distinction between them is subtle, as no objective differences in symptoms or treatment response have been shown based solely on the presence or absence of sleep-onset rapid eye movement periods in the MSLT.[3] Patients with idiopathic hypersomnia exhibit true hypersomnia, with sleep time of more than 11 h in 24 h and persistent sleepiness during the day in association with sleep inertia.[45] It is possible that the cause of idiopathic hypersomnia with prolonged sleep time is distinct, but the exclusion of sleep deprivation is required, mandating long sleep recordings in standardised conditions to support this diagnosis.[30,45] The severity of NT1, NT2, and idiopathic hypersomnia can be assessed by validated self-report questionnaires to monitor and optimise disease management.[46,47]

Periodic hypersomnia and Kleine–Levin syndrome should also be mentioned in this Series paper. In Kleine–Levin syndrome, patients are usually children or young adolescents, most often male, who suddenly have substantial (often >18 h of sleep per day) and

Panel 3: **Diagnostic criteria and characteristics of narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia**

Narcolepsy type 1 (NT1)

EDS for longer than 3 months, associated with either:

- Cataplexy, mean sleep latency of less than or equal to 8 min on the multiple sleep latency test (MSLT), and at least two sleep onset rapid eye movement periods (SOREMPs) within 15 min of falling asleep during MSLT or polysomnography
- Cerebrospinal fluid hypocretin concentration less than 110 pg/mL

Narcolepsy type 2 (NT2)

EDS for longer than 3 months, without cataplexy, plus both:

- Mean sleep latency on the MSLT of less than or equal to 8 min and at least two SOREMPs on MSLT or polysomnography
- Cerebrospinal fluid hypocretin concentration of more than 110 pg/mL or not measured

The complaint of EDS cannot be better explained by another cause, such as sleep deprivation, sleep apnoea syndrome, circadian rhythm disorders, the effect of a medication, or substance abuse.

If cataplexy appears or if hypocretin concentrations appear to be less than 110 pg/mL, then the condition should be reclassified as NT1.

Idiopathic hypersomnia

EDS for longer than 3 months, without cataplexy, with MSLT and polysomnography showing no more than one SOREMP and one or both of:

- Mean sleep latency on the MSLT of less than or equal to 8 min
- Total sleep time more than 11 h on a continued 24 h polysomnography recording or by wrist actigraphy in association with a sleep diary (averaged during at least 7 days with unrestricted sleep)

Insufficient sleep syndrome should be excluded first. Both EDS symptoms and MSLT findings cannot be more clearly attributed to another sleep disorder, a medical or psychiatric disorder, or the use of drugs or medications.

abrupt onset episodes of hypersomnia lasting usually 1–2 weeks.[48] Memory of the episodes is typically absent or reduced, and the patient returns to unaffected daily behaviour between episodes. The hypersomnia does not occur in isolation, as the patient also exhibits cognitive alterations when awake, such as feeling out of place, being unable to talk, or answering only in monosyllables, a phenotype sometimes associated with disinhibition that leads to megaphagia or inappropriate sexual behaviour. A genetic study suggested that Kleine–Levin syndrome shares genetic architecture with bipolar disorder and circadian disturbances, and is associated with reports of birth difficulties,[49] possibly explaining the beneficial effect of lithium in approximately 50% of people with Kleine–Levin syndrome.

Neurological disorders

EDS is an associated symptom that occurs in several neurological disorders. Variable frequencies of EDS are reported as a result of different studied populations and heterogeneous methodology between studies (due to different definitions and means of assessing EDS). Neurological disorders can affect the brain to generate sleep, wake, and circadian functions.

In Alzheimer's disease, EDS and napping are frequent, which could be related to sleep disruption with extended periods of wakefulness at night, circadian alterations, and concomitant obstructive sleep apnoea.[50–52] Patients with Parkinson's disease, the most common synucleinopathy, often report EDS and sleep attacks, which are mainly a consequence of intrinsic alterations of sleep–wake structures due to neurodegeneration and dopaminergic drugs.[51] Additionally, depression, insomnia, obstructive sleep apnoea, circadian alterations, and sedative drugs can also contribute to EDS.[53] In 10–20% of patients with Parkinson's disease, the MSLT shows reduced mean sleep latencies and rarely shows narcolepsy-like findings.[54] EDS with frequent napping is also commonly seen in patients with other synucleinopathies, such as dementia with Lewy bodies, in whom degeneration of CNS structures modulating sleep might occur.[51]

EDS after stroke has been mostly studied in the context of sleep-disordered breathing.[55,56] Although sleep-disordered breathing can be considered a main factor leading to EDS, other factors, such as comorbid depression, use of medications with sedative effects, reduction of physical activity, and cerebrovascular involvement of strategic areas, can all influence development of EDS. True hypersomnia can also be reported after stroke, whether associated with EDS or not. Importantly, sleep alterations can have deleterious effects in patients with stroke, with worse poststroke functional outcomes in patients with hypersomnia or EDS than in patients without this disorder or symptom.[56–58]

EDS is common after a traumatic brain injury, occurring in up to a third of patients, but this symptom might be under-reported in contrast to the main complaint of insomnia.[59] EDS in this context might be directly related to traumatic damage of wake-promoting brain areas. The MSLT might show reduced mean sleep latencies and narcolepsy-like findings up to 6 months after traumatic brain injury. High sleep needs seem to correlate with more severe traumatic brain injuries and the presence of intracranial haemorrhage.[59] EDS and hypersomnia after traumatic brain injury can impair the functional recovery of patients.[60]

Although less prevalent than fatigue, EDS is also reported by 20–25% of patients with multiple sclerosis.[61] Sleep-related disturbances, such as obstructive sleep

apnoea, restless legs syndrome, and insomnia, have been mentioned as possible factors contributing to EDS in patients with multiple sclerosis.[62]

Other CNS damage due to infection, tumours, or neurodegeneration in particular regions, such as the hypothalamus, thalamus, or brainstem, can induce EDS.

Other medical disorders

EDS is commonly reported by patients with chronic non-neurological conditions. Some genetic disorders, such as Niemann–Pick type C disease, Prader–Willi syndrome, Smith–Magenis syndrome, and myotonic dystrophy,[63] are often associated with severe EDS, narcolepsy-cataplexy, or hypersomnia, which might also be related to obstructive sleep apnoea.

In patients with cancer, several causes have been proposed for the occurrence of EDS, including cancer therapies, other medications with sedative effects, comorbid mood disturbances, and underlying sleep disorders such as obstructive sleep apnoea.[64] The presence of EDS in patients with chronic kidney disease is also multifactorial. Specifically in patients receiving dialysis, a reduction in total sleep times, poor sleep quality, and high frequencies of obstructive sleep apnoea and restless legs syndrome have been described. However, other factors, such as mood disturbances and polypharmacy, can also contribute to the occurrence of EDS.[65,66] EDS has also been reported as a common symptom in a range of liver conditions and endocrine conditions, with EDS severity correlated with metabolic encephalopathy.[67] A substantial and increasing prevalence of EDS is found in respiratory conditions, such as chronic obstructive pulmonary disease, due to concomitant obstructive sleep apnoea or the presence of nocturnal hypoventilation.[68] In other groups of patients, such as patients with chronic rheumatic conditions, difficulties in differentiating fatigue from EDS have been highlighted and it is postulated that a proportion of patients reporting fatigue might actually be excessively sleepy.[69]

Psychiatric disorders

The complaint of EDS is very frequent in psychiatric disorders, especially in mood disorders, particularly major depressive disorder, bipolar disorder, and seasonal affective disorder. However, the precise frequency of EDS in psychiatric disorders remains difficult to establish due to various definitions of EDS, which sometimes overlap with other hypersomnolence symptoms, and the various tests used in studies that lead to heterogeneous findings.[70] The frequency of hypersomnolence symptoms (eg, EDS with long but non-refreshing naps, extended nocturnal sleep, and sleep inertia) in major depressive disorder varies greatly across studies, with an age and sex effect (being higher in women than in men) and with prevalence ranging from 9% in children to 76% in adults.[71] Few studies have investigated hypersomnolence in major depressive disorder with objective measures, such as the MSLT or continuous polysomnography. A meta-analysis showed that patients with major depressive disorder with hypersomnolence complaints evaluated with the MSLT showed mean sleep latencies similar to normative values.[72] Another study comparing night-time sleep duration during a 2-day protocol in psychiatric hypersomnia (mainly patients with major depressive disorder) and in idiopathic hypersomnia revealed that only 14% of patients with psychiatric hypersomnia slept longer than 9 h, with a lower sleep duration than in idiopathic hypersomnia (7·68 h *vs* 9·92 h).[73] Hypersomnolence symptoms are also frequent in patients with type 1 or type 2 bipolar disorder, with prevalence ranging from 23% to 78%.[74] One study assessing sleepiness with the MSLT in patients with bipolar disorder and depression with hypersomnolence complaints did not report objective EDS.[74] Hypersomnolence is also one of the major features of seasonal affective disorder, with prevalence varying from 67% to 76%.[75] Most of the studies assessing EDS in patients with psychiatric disorders did not use validated tests to assess hypersomnolence, and substantial discrepancies between self-reported and objective EDS have been shown. These discrepancies between self-reported and objective EDS data raise the question of whether fatigue and apathy are misperceived or whether clinophilia is misreported as EDS or hypersomnolence by patients with depression.[70,71] Sleep attacks of a dissociative nature might also be diagnosed in psychiatric disorders. However, the number of complaints of EDS is high in mood disorders and seems to be associated with poor prognosis, resistance to treatment, increased risk for relapse and suicide, and functional impairment. As an additional complication for the assessment of EDS, psychiatric disorders can be comorbid with central disorders of hypersomnolence, such as narcolepsy. Furthermore, iatrogenic causes of EDS (eg, sedative medications) and obstructive sleep apnoea should be excluded.[71]

Children with attention-deficit hyperactivity disorder (ADHD) have higher EDS, more movements in sleep, and a higher apnoea-hypopnoea index than do children without ADHD.[76] EDS and other hypersomnolence symptoms are reported in half of adult patients with ADHD,[77] with a high frequency of ADHD and ADHD-like symptoms in patients with central hypersomnolence disorders. The nature of the link between EDS, inattention, and hyperactivity is complex and might involve both a cause–effect relationship and intrinsic features of a similar neurodevelopmental dysfunction.

Medications

The use of polypharmacy is not unusual, especially in patients with several chronic conditions and in patients older than 65 years who often have to take multiple medications.[78] Several of the medications commonly used in clinical practice can affect sleep and lead to EDS (appendix p 3). EDS can also occur because of use of

alcohol and cannabis, or because of discontinuation of stimulants. People who consume a large amount of caffeine might complain of EDS if they stop their caffeine intake.

Pathophysiology of EDS

EDS can be explained from a physiological, neuroanatomical, or neurochemical perspective (panel 4, figure 2).

Consequences of EDS

The consequences of EDS for the individual and at the societal level are well established. There is an increased risk of road traffic accidents, negative effects on professions, and negative effects on education in children. Sleepiness when driving is understandably a major public concern. The proportion of road traffic accidents that occur as a consequence of sleepiness varies between countries, but it has been reported to be the cause for up

Panel 4: Pathophysiology of excessive daytime sleepiness (EDS)

At the physiological level, EDS is most commonly analysed in relation to circadian timing (the internal clock) and insufficient sleep (sleep debt).

EDS increases with sleep deprivation and insufficient sleep but is also modulated by the activity of the suprachiasmatic nucleus, which functions as an internal clock. The effect of this circadian clock, however, does not occur homogeneously during the day and night, but is delayed in relation to the time of waking up and the time of sleep onset.[79] Specifically, wake is promoted by the suprachiasmatic nucleus in the afternoon and evening (in association with a rise in body temperature), whereas sleep is facilitated by the circadian clock in the early morning (in association with a drop in body temperature) as a function of the circadian rhythm. In healthy individuals, the relationship between circadian effects and sleep-debt-driven effects is optimal for daily functioning. Once an individual wakes up, they are rested and awake because they have no sleep debt. As the day progresses, their sleep debt increases but is compensated by a wake-promoting signal coming from the suprachiasmatic nucleus.[79] This second wake-promoting signal allows individuals to stay awake in the afternoon, even when they have been awake for many hours. At night, the opposite happens. Sleep is high in slow-wave sleep during the first part of the night as the individual catches up on their daily sleep debt, whereas in the second part of the night, the individual stays asleep because the temperature drops further. This second part of the night has a high proportion of rapid eye movement (REM) sleep, which is strongly regulated by the circadian clock.[80]

A misalignment of the circadian clock and insufficient or disturbed sleep can cause EDS. This process is best seen in individuals with jet lag, shift workers, or in individuals with a delayed clock (known as night owls). A delayed clock is a frequent occurrence in adolescence; individuals are naturally most awake late at night and, as a consequence, if there is a need to work early they will be sleep deprived during the day and most sleepy in the morning hours.

Neuroanatomically, the main brain regions where lesions have been involved in producing sleepiness have been the thalamus (bilateral lesions notably of the paramedian nuclei because of a stroke),[81] the posterior hypothalamus (as reported in encephalitis lethargica) where hypocretin and histaminergic cells are located,[82] and the brainstem. Thalamic lesions are associated with a particular phenotype sometimes called subwakefulness syndrome. Regions in the brainstem, such as the ventrolateral periaqueductal gray, have been shown to regulate REM sleep by inhibiting glutamatergic neurons located in the sublaterodorsal tegmental nucleus. These brainstem regions are important to the pathophysiology of cataplexy and REM sleep behaviour disorder.[83]

Neuroimaging studies have supported the role of particular brain regions involved in sleepiness. Sleep deprivation showed reduced regional cerebral glucose metabolism, especially in the thalamus, the temporal, prefrontal, and anterior cingulate cortices, the basal ganglia, and limbic regions.[84] Functional neuroimaging studies have shown that EDS is associated with increased activity in the default mode network, a network most active during wakeful rest and suppressed during goal-directed tasks. However, neuroimaging data are not always conclusive as changes in brain activity also depend on the behavioural loss imposed on sleepy patients, and on the cause of EDS.[85]

At the neurochemical level, several neurotransmitters are involved in sleep regulation and, as a consequence, can be involved in EDS.[82] The brain circuitry controlling wake and sleep depends on fast neurotransmitters, such as glutamate and γ-aminobutyric-acid (GABA), with opposing effects on wakefulness being interconnected with the classic monoaminergic, cholinergic, and peptidergic modulatory systems. Increased GABAergic transmission is the most common mode of action of currently used sedating hypnotics (such as benzodiazepines). Monoaminergic neurons that drive arousal produce norepinephrine, serotonin, dopamine, or histamine. With the exception of dopamine cells, monoaminergic neurons that drive arousal share similar firing patterns among themselves, with high firing rates during wake, slow firing rates during non-REM sleep, and almost no firing rates during REM sleep. Cholinergic systems are both active in wake and REM sleep. Two hypothalamic neuropeptide systems, melanin-concentrating hormone and orexin, also play a crucial role in the regulation of wake and REM sleep. Adenosine seems to be a strong measure of sleep homoeostasis; accumulation of adenosine in the basal forebrain is a function of extended wakefulness and decreases with sleep duration.

The precise neurobiology and neural basis of EDS is only partly known, and probably involves many neurochemical and electrophysiological circuits.[86]

to a third of traffic accidents overall.[89,90] Sleep deprivation is the main factor associated with EDS and road traffic accidents that are narrowly avoided.[91–93] Sleep deprivation leading to EDS and drowsy driving might occur in specific circumstances, such as shift work.[94] Another subgroup of particular interest is patients with obstructive sleep apnoea. Untreated confirmed obstructive sleep apnoea[95] and suspected obstructive sleep apnoea[91,96] have been associated with an increased risk of traffic accidents, and traffic accidents that are narrowly avoided, due to sleepiness. Furthermore, drivers who are non-adherent to obstructive sleep apnoea treatment are 5-times more likely to have a serious, preventable road traffic accident.[97] As EDS is the core symptom of central disorders of hypersomnolence, these disorders could lead to sleepiness while driving. A French study reported an increased frequency of road traffic accidents in patients with central disorders of hypersomnolence when compared with healthy control individuals regardless of treatment status at inclusion. However, this risk did not differ between patients treated for at least 5 years and healthy individuals.[98] In children affected by central disorders of hypersomnolence (eg, narcolepsy), missed school days, lower grades, poorer quality of life (in school and social functioning domains), and behavioural issues (issues with attention, or ADHD) are reported more frequently than in healthy children.[99,100]

EDS is also relevant when considering daytime functioning at work and quality of life, as it is often associated with reduced academic or professional performance and domestic or work accidents.[101] The occurrence of EDS is important in people who drive, as shown previously, but also in health-care professionals who are usually exposed to shift work and sleep deprivation. A high proportion of junior doctors report having EDS, which correlates negatively with quality of health.[102] Patients with obstructive sleep apnoea and EDS show reduced quality of life and more impairment to productivity than non-sleepy obstructive sleep apnoea patients and control individuals.[103,104] EDS also affects reduced quality of life in narcolepsy.[105]

EDS might be also associated with an increased risk of morbidity and mortality related to cardiovascular, psychiatric, and neurodegenerative pathologies, also independently of standard pathophysiological consequences of primary disorders producing EDS. Patients with obstructive sleep apnoea with EDS had a higher baseline prevalence of and a higher risk of incident or recurrent hypertension, diabetes, cardiovascular events,[106] and mortality[107,108] than patients with obstructive sleep apnoea subtypes with predominant disturbed sleep and minimal or no sleepiness symptoms. EDS is also associated with increased risk of cardiovascular morbidity and mortality in the general population, particularly people older than 65 years. Older people with no history of cardiovascular diseases who reported experiencing EDS frequently had an increased risk of coronary heart disease

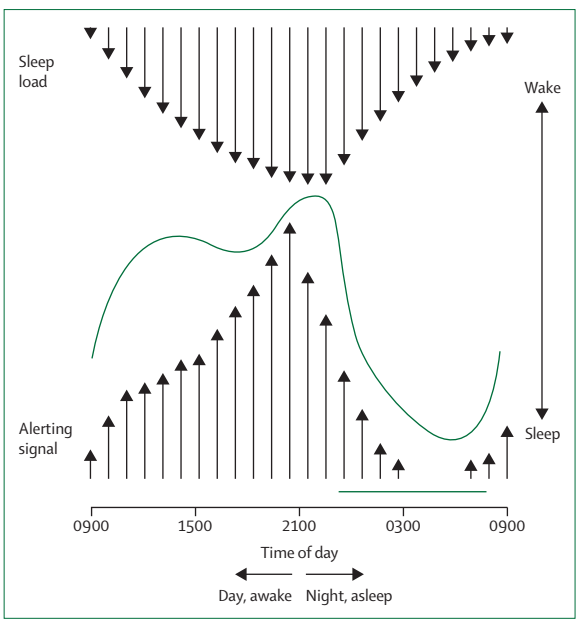

Figure 2: **Sleep and circadian physiology interacting to maintain wakefulness during the day and to control sleep during the night**
Reproduced from Edgar,[87,88] by permission of Backhuys Publishers.

and stroke during a median follow-up of 5 years compared with people without EDS.[109,110] In the same study, EDS was associated with an increased risk of cardiovascular mortality but not an increased risk of cancer-related mortality during 6 years of follow-up.[111] Results of studies of EDS that include adults aged 32–69 years are often consistent with results of studies that only include older community-dwelling participants.[112,113] The mechanisms whereby EDS increases cardiovascular risk remain unclear. However, inflammatory cytokines and oxidative stress (potential mechanisms that remain understudied in humans) might be the link between EDS and cardiovascular risk.

Similarly, EDS and prolonged daytime naps have been associated with increased risk of cognitive decline and neurodegenerative conditions, such as Alzheimer's disease.[114] A prospective study showed that men who napped for more than 2 h per day were 66% more likely to develop cognitive impairment in the 12 years when cognition was repeatedly assessed than those who napped for less than 30 min per day,[115] and cognitive decline was found to be more rapid in long sleepers (≥ 9h of total daily sleep) compared with the reference group (total daily sleep 6–8 h).[116] The relationship between sleep disruption and dementia has become more closely scrutinised in the past decade, partly driven by the discovery of the glymphatic system of the brain and the sleep-dependent role of this system in the clearance of metabolites, including amyloid β.[117] However, the nature of the association between sleepiness and Alzheimer's disease remains uncertain. EDS could be a symptom of other sleep disorders, such as obstructive sleep

apnoea, which might lead to cognitive decline through intermittent hypoxia, neuroinflammation, decreased glymphatic clearance, and direct disruption of deep and rapid eye movement (REM) sleep. Additionally, sleep can be disrupted in preclinical phases of Alzheimer's disease and other neurodegenerative disorders.[118]

Management of EDS

As the underlying causes of EDS are highly heterogeneous, there are multiple treatment options. The initial stage in the management of EDS should focus on addressing sleep disruption or sleep restriction if feasible.

Non-pharmacological or behavioural treatment can often suffice, particularly when the cause of EDS is chronic sleep restriction. Sleep education and sleep hygiene advice might be enough for a patient to recognise that the basis of their sleepiness is insufficient sleep, and that prioritising sleep over work-related activities or social activities will resolve their daytime symptoms. Circadian rhythm disorders can be more challenging to treat than chronic sleep restriction.[10] Shift-work disorder is common, but management of this disorder depends on employers to develop shift work patterns that do not lead to sleep loss or circadian disruption. Some people are not able to do shift work without developing serious health issues (including EDS) and, therefore, should consider an alternative job when possible. Strict adherence to sleep hygiene measures, such as restriction of light exposure before bed and avoidance of excessive stimulant use, could facilitate better-quality sleep than if sleep hygiene measures are not adhered to. For individuals with delayed sleep–wake phase disorder or, less commonly, advanced sleep–wake phase disorder, behavioural interventions accompanied by cues influencing the circadian rhythm, such as appropriately timed melatonin and light therapy, are necessary.

Identification of other medical issues contributing to fragmented sleep (such as pain, restless legs, immobility, bladder discomfort, nocturnal breathlessness, or mood disorders) can also provide alternative strategies for improving sleep quality and reducing sleep disruption. A review of prescribed and non-prescribed medications should also be done, as medications are frequently the cause of EDS (appendix p 3). For patients with obstructive sleep apnoea that are overweight or obese, weight loss can be helpful. A loss of 20% of the baseline weight of an individual is associated with a 50% reduction in apnoea-hypopnoea index.[119] However, in practice, sustained weight reduction is not always efficient, even after bariatric surgery. Further management options that could help patients with obstructive sleep apnoea include avoiding sedating medications, avoiding alcohol, and positional manoeuvres that keep patients in a non-supine position as obstructive sleep apnoea is often worse when supine than when in other positions. However, the gold standard of treatment for obstructive sleep apnoea is CPAP or automated positive airway pressure (APAP) therapy, both of which pneumatically splint the airway and prevent collapse of the airway. CPAP or APAP therapy can be extremely successful at treating obstructive sleep apnoea but are not always tolerated, with up to a third of obstructive sleep apnoea patients being non-adherent.[120] Alternative strategies include forward displacement of the mandible through the use of mandibular advancement devices or, for some patients, surgery to address anatomical contributors to obstructive sleep apnoea. Interest has increased in both implanted hypoglossal nerve stimulation and transcutaneous hypoglossal nerve stimulation,[121] although these technologies remain in their infancy and their use is not yet widespread.

For patients with central hypersomnolence disorders, such as narcolepsy and idiopathic hypersomnia, the mainstays of treatment are wake-promoting agents and stimulant drugs to promote wakefulness.[122] Although these drugs improve EDS, they do not usually bring subjective or objective measures of sleepiness within the normal range. These drugs can also be used occasionally for indications other than central hypersomnolence disorders under specialist care. Historically, wake-promoting agents have been restricted to modafinil, and stimulants have been restricted to methylphenidate and amphetamine-based drugs (eg, dexamfetamine). Modafinil (and the R-isomer of racemic modafinil, armodafinil) is generally considered a wake-promoting agent rather than a classic psychostimulant. The precise mechanism of action of modafinil is debated, but it might work as a weak dopamine reuptake inhibitor and therefore increase wakefulness.[123] Modafinil is often considered to be a first-line treatment for central hypersomnolence disorders, and in some countries it is used in shift-work disorder and obstructive sleep apnoea (although in Europe these disorders are not approved indications). Modafinil is generally safe and has low potential for overuse. Methylphenidate and amphetamine-based agents (off-label in many European countries) have a range of pharmacodynamic effects, resulting in enhanced dopaminergic activities, noradrenergic activities, and serotoninergic activities. This broad spectrum of neuropharmacological changes explains why wakefulness is not the only effect of these drugs, and also explains why they have potential behavioural, addictive, hypertension, and cardiovascular consequences.[124,125] Sodium oxybate, a short-acting γ-aminobutyric-acid ($GABA_B$) receptor agonist, is another widely used agent in narcolepsy. It acts primarily as a CNS depressant, consolidating the disturbed night-time sleep of narcolepsy and improving EDS and cataplexy in adults and children.[126] Since 2020, a low-sodium version of sodium oxybate has been approved for use by the US Food and Drug Administration to treat narcolepsy, cataplexy, and EDS in idiopathic hypersomnia.[127] A slow-release formulation of sodium oxybate that is taken each night was developed

in 2022.[128] This formulation showed significant improvement in narcolepsy symptoms of patients with narcolepsy.

In the past 5 years, the armamentarium of treatments for EDS has substantially expanded worldwide.[123] Novel agents include pitolisant, a histamine-3 receptor antagonist or inverse agonist that increases histamine with a resultant wake-promoting effect and some efficacy on reducing cataplexy.[129] Since 2020, solriamfetol, a noradrenaline-dopamine reuptake inhibitor, has been licensed across multiple locations (eg, Europe and the USA) as a wake-promoting agent for narcolepsy.[130] European and American guidelines published in 2021 provided a detailed summary of the evidence assessing the best management of narcolepsy in both adults and children.[131,132] When wake-promoting pharmacological agents are appropriate, the choice of prescribed drug is dependent on the side-effect profile, associated symptoms, severity of associated symptoms, comorbid conditions or disorders, local prescription protocols, and financial considerations. For NT1, normalising the hypocreting pathway would be the definitive aim of treatment. However, attempts to normalise the hypocretin pathway have been largely unsuccessful, except for encouraging preliminary data for hypocretin receptor-2 agonists (NCT04096560). Pitolisant and solriamfetol were tested as adjuncts to CPAP therapy for patients with obstructive sleep apnoea with residual sleepiness despite good CPAP adherence. Both drugs significantly reduced subjective and objective sleepiness in these patients[133,134] and licenses were obtained in the EU and the USA for treatment. Pitolisant also reduced daytime sleepiness in sleepy patients with obstructive sleep apnoea who refused or were non-adherent to CPAP.[135]

Conclusions and future directions

EDS has been historically under-recognised, under-appreciated, and understudied. Sleep disorders are associated with high expenses and frequent use of health-care services. Historically, the main focus of the consequences of EDS has been on quality of life and socioeconomic burden. Nowadays, however, the relevance of EDS as a feature of behavioural and biological sleep disorders; as a feature of other medical and psychiatric conditions; as a confounder of treatment response in a range of diseases; as a risk factor for poor cardiovascular, neurological, and psychiatric outcomes; and as a potential predictive symptom of neurodegeneration has been shown. The complex relationship between EDS and several medical conditions highlights the importance of collaborative work between sleep specialists and other health-care professionals, including psychiatrists, to improve care of patients with EDS.

There is a need to identify biomarkers of EDS and to increase understanding of the neurobiology of EDS to better diagnose and treat patients. However, due to the multiple dimensions of EDS resulting from the balance between the capacity to stay awake and the propensity to fall asleep, there is no gold-standard measurement of excessive sleepiness and no quantifiable biological markers of excessive sleepiness. A rigorous clinical approach and appropriate investigation of EDS are necessary. Technological advances in the past 5 years have shown it might be possible to measure polysomnographic sleep in large populations for long durations, and to find proxy blood biomarkers of sleep debt, circadian phase, or specific sleep disorders. These technological advances indicate the possibility of answering the most important questions in sleep medicine, such as questions regarding the molecular basis of sleep or sleep disorders, and have substantial applications for individual and population health.

Further research is also necessary to gather epidemiological data concerning the genetic and environmental risk factors of patients with EDS, and to improve the pathophysiological understanding of the different pathologies of hypersomnolence disorders. Patients with EDS should be screened for a timely diagnosis of hypersomnolence disorders and to improve treatment initiation, not only at a pharmacological level but also considering the educational, social, and professional needs of patients.

Contributors

All authors contributed equally to the conception of the article, the design of the article, data collection, drafting the article, revision of the article, and final approval of the version to be published.

Declaration of interests

LP-C received funds for educational sessions delivered for Jazz Pharmaceuticals. EM received funds for research projects, clinical trial projects, seminars, board engagements, and travel to conferences from Jazz Pharmaceuticals, Orexia, Idorsia, Takeda, Avadel, Harmony, Dreem, Apple, Huami, Sunovion, and Axsome. GL received speaker fees for Takeda, consultancy fees for Eisai, and institutional income from Bioprojet and Jazz. YD received funds for seminars, board engagements, and travel to conferences from UCB Pharma, Jazz Pharmaceuticals, Idorsia, Takeda, Avadel, and Bioprojet.

References

1 American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 3rd edn. Darien, IL: American Academy of Sleep Medicine, 2014.
2 Sateia MJ. International Classification of Sleep Disorders-Third Edition. *Chest* 2014; **146:** 1387–94.
3 Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. *Sleep Med Rev* 2020; **52:** 101306.
4 Berkowski JA, Shelgikar AV. Disorders of excessive daytime sleepiness including narcolepsy and idiopathic hypersomnia. *Sleep Med Clin* 2016; **11:** 365–78.
5 Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004; **363:** 978–88.
6 Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cereb Cortex* 2006; **16:** 916–28.
7 Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Res* 2005; **14:** 245–53.
8 Sommerauer M, Valko PO, Werth E, Baumann CR. Excessive sleep need following traumatic brain injury: a case-control study of 36 patients. *J Sleep Res* 2013; **22:** 634–39.

9 Perlis ML, Posner D, Riemann D, Bastien CH, Tell J, Thase M. Insomnia. *Lancet* 2022; published online Sept 14. https://doi.org/10.1016/S0140-6736(22)00879-0.

10 Meyer N, Harvey AG, Lockley SW, Dijk D-J. Circadian rhythms and disorders of the timing of sleep. *Lancet* 2022; published online Sept 14. https://doi.org/10.1016/S0140-6736(22)00877-7.

11 Siegel JM. Sleep function: an evolutionary perspective. *Lancet Neurol* 2022; **21:** 937–46.

12 Jaussent I, Morin CM, Ivers H, Dauvilliers Y. Incidence, worsening and risk factors of daytime sleepiness in a population-based 5-year longitudinal study. *Sci Rep* 2017; **7:** 1372.

13 Theorell-Haglöw J, Åkerstedt T, Schwarz J, Lindberg E. Predictors for development of excessive daytime sleepiness in women: a population-based 10-year follow-up. *Sleep* 2015; **38:** 1995–2003.

14 Jaussent I, Morin CM, Ivers H, Dauvilliers Y. Natural history of excessive daytime sleepiness: a population-based 5-year longitudinal study. *Sleep* 2020; **43:** zsz249.

15 Ohayon MM. From wakefulness to excessive sleepiness: what we know and still need to know. *Sleep Med Rev* 2008; **12:** 129–41.

16 Berger M, Hirotsu C, Haba-Rubio J, et al. Risk factors of excessive daytime sleepiness in a prospective population-based cohort. *J Sleep Res* 2021; **30:** e13069.

17 Fernandez-Mendoza J, Vgontzas AN, Kritikou I, Calhoun SL, Liao D, Bixler EO. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. *Sleep* 2015; **38:** 351–60.

18 Calhoun SL, Vgontzas AN, Fernandez-Mendoza J, et al. Prevalence and risk factors of excessive daytime sleepiness in a community sample of young children: the role of obesity, asthma, anxiety/depression, and sleep. *Sleep* 2011; **34:** 503–07.

19 Liu Y, Zhang J, Li SX, et al. Excessive daytime sleepiness among children and adolescents: prevalence, correlates, and pubertal effects. *Sleep Med* 2019; **53:** 1–8.

20 Merdad RA, Akil H, Wali SO. Sleepiness in adolescents. *Sleep Med Clin* 2017; **12:** 415–28.

21 Moreira GA, Pradella-Hallinan M. Sleepiness in children. *Sleep Med Clin* 2017; **12:** 407–13.

22 Ohayon MM. Operational definitions and algorithms for excessive sleepiness in the general population: implications for DSM-5 nosology. *Arch Gen Psychiatry* 2012; **69:** 71.

23 Ohayon MM, Reynolds CF, Dauvilliers Y. Excessive sleep duration and quality of life: excessive sleep in USA. *Ann Neurol* 2013; **73:** 785–94.

24 Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991; **14:** 540–45.

25 Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1986; **9:** 519–24.

26 Arand DL, Bonnet MH. The multiple sleep latency test. *Handb Clin Neurol* 2019; **160:** 393–403.

27 Kendzerska TB, Smith PM, Brignardello-Petersen R, Leung RS, Tomlinson GA. Evaluation of the measurement properties of the Epworth Sleepiness Scale: a systematic review. *Sleep Med Rev* 2014; **18:** 321–31.

28 Basille D, Baud ME, Andrejak C, Basille-Fantinato A, Jounieaux V. Correlation between the Epworth Sleepiness Scale and the Maintenance of Wakefulness Test in obstructive sleep apnea patients treated with positive airway pressure. *Respir Med Res* 2020; **78:** 100787.

29 Evangelista E, Lopez R, Barateau L, et al. Alternative diagnostic criteria for idiopathic hypersomnia: a 32-hour protocol. *Ann Neurol* 2018; **83:** 235-47.

30 Evangelista E, Lopez R, Barateau L, et al. Alternative diagnostic criteria for idiopathic hypersomnia: a 32-hour protocol: idiopathic hypersomnia. *Ann Neurol* 2018; **83:** 235–47.

31 Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* 2003; **26:** 342–92.

32 Evangelista E, Rassu AL, Lopez R, et al. Sleep inertia measurement with the psychomotor vigilance task in idiopathic hypersomnia. *Sleep* 2022; **45:** zsab220.

33 Consensus Conference Panel, Watson NF, Badr MS, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *J Clin Sleep Med* 2015; **11:** 591–92.

34 Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019; **7:** 687–98.

35 Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med* 2019; **380:** 1442–49.

36 Gasa M, Tamisier R, Launois SH, et al. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res* 2013; **22:** 389–97.

37 Pepin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J* 2009; **33:** 1062–67.

38 Vgontzas AN, Bixler EO, Tan TL, Kantner D, Martin LF, Kales A. Obesity without sleep apnea is associated with daytime sleepiness. *Arch Intern Med* 1998; **158:** 1333–37.

39 Manconi M, Garcia-Borreguero D, Schormair B, et al. Restless legs syndrome. *Nat Rev Dis Primers* 2021; **7:** 80.

40 Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy—clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol* 2019; **15:** 519–39.

41 Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000; **6:** 991–97.

42 Kornum BR, Faraco J, Mignot E. Narcolepsy with hypocretin/orexin deficiency, infections and autoimmunity of the brain. *Curr Opin Neurobiol* 2011; **21:** 897–903.

43 Maski K, Mignot E, Plazzi G, Dauvilliers Y. Disrupted nighttime sleep and sleep instability in narcolepsy. *J Clin Sleep Med* 2022; **18:** 289–304.

44 Bourgin P, Zeitzer JM, Mignot E. CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol* 2008; **7:** 649–62.

45 Leu-Semenescu S, Quera-Salva M-A, Dauvilliers Y. French consensus. Idiopathic hypersomnia: investigations and follow-up. *Rev Neurol (Paris)* 2017; **173:** 32–37.

46 Dauvilliers Y, Beziat S, Pesenti C, et al. Measurement of narcolepsy symptoms: the Narcolepsy Severity Scale. *Neurology* 2017; **88:** 1358–65.

47 Dauvilliers Y, Evangelista E, Barateau L, et al. Measurement of symptoms in idiopathic hypersomnia: the Idiopathic Hypersomnia Severity Scale. *Neurology* 2019; **92:** e1754–62.

48 Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine–Levin syndrome: a systematic review of 186 cases in the literature. *Brain* 2005; **128:** 2763–76.

49 Ambati A, Hillary R, Leu-Semenescu S, et al. Kleine–Levin syndrome is associated with birth difficulties and genetic variants in the *TRANK1* gene loci. *Proc Natl Acad Sci USA* 2021; **118:** e2005753118.

50 Gaig C, Iranzo A. Sleep-disordered breathing in neurodegenerative diseases. *Curr Neurol Neurosci Rep* 2012; **12:** 205–17.

51 Iranzo A. Sleep in neurodegenerative diseases. *Sleep Med Clin* 2016; **11:** 1–18.

52 Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. *Sleep Med Rev* 2015; **19:** 29–38.

53 Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *Lancet Neurol* 2018; **17:** 559–68.

54 Arnulf I, Konofal E, Merino-Andreu M, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology* 2002; **58:** 1019–24.

55 Pérez-Carbonell L, Bashir S. Narrative review of sleep and stroke. *J Thorac Dis* 2020; **12:** S176–90.

56 Baillieul S, Dekkers M, Brill A-K, et al. Sleep apnoea and ischaemic stroke: current knowledge and future directions. *Lancet Neurol* 2022; **21:** 78–88.

57 Hermann DM, Bassetti CL. Role of sleep-disordered breathing and sleep–wake disturbances for stroke and stroke recovery. *Neurology* 2016; **87:** 1407–16.

58 Harris AL, Elder J, Schiff ND, Victor JD, Goldfine AM. Post-stroke apathy and hypersomnia lead to worse outcomes from acute rehabilitation. *Transl Stroke Res* 2014; **5:** 292–300.

59 Imbach LL, Valko PO, Li T, et al. Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. *Brain* 2015; **138:** 726–35.

60 Sandsmark DK, Elliott JE, Lim MM. Sleep–wake disturbances after traumatic brain injury: synthesis of human and animal studies. *Sleep* 2017; **40:** zsx044.

61 Popp RFJ, Fierlbeck AK, Knüttel H, et al. Daytime sleepiness versus fatigue in patients with multiple sclerosis: a systematic review on the Epworth Sleepiness Scale as an assessment tool. *Sleep Med Rev* 2017; **32:** 95–108.

62 Brass SD, Li C-S, Auerbach S. The underdiagnosis of sleep disorders in patients with multiple sclerosis. *J Clin Sleep Med* 2014; **10:** 1025–31.

63 Dauvilliers YA, Laberge L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. *Sleep Med Rev* 2012; **16:** 539–45.

64 Jaumally BA, Das A, Cassell NC, et al. Excessive daytime sleepiness in cancer patients. *Sleep Breath* 2021; **25:** 1063–67.

65 So JY, Warburton KM, Rosen IM. A guide to management of sleepiness in ESKD. *Am J Kidney Dis* 2020; **75:** 782–92.

66 Nigam G, Camacho M, Chang E, Riaz M. Exploring sleep disorders in patients with chronic kidney disease. *Nat Sci Sleep* 2018; **10:** 35–43.

67 Shah NM, Malhotra AM, Kaltsakas G. Sleep disorder in patients with chronic liver disease: a narrative review. *J Thorac Dis* 2020; **12:** S248–60.

68 Shah NM, Murphy PB. Chronic obstructive pulmonary disease and sleep: an update on relevance, prevalence and management. *Curr Opin Pulm Med* 2018; **24:** 561–68.

69 Mahowald ML, Mahowald MW. Nighttime sleep and daytime functioning (sleepiness and fatigue) in well-defined chronic rheumatic diseases. *Sleep Med* 2000; **1:** 179–93.

70 Plante DT, Finn LA, Hagen EW, Mignot E, Peppard PE. Subjective and objective measures of hypersomnolence demonstrate divergent associations with depression among participants in the Wisconsin Sleep Cohort Study. *J Clin Sleep Med* 2016; **12:** 571–78.

71 Barateau L, Lopez R, Franchi JAM, Dauvilliers Y. Hypersomnolence, hypersomnia, and mood disorders. *Curr Psychiatry Rep* 2017; **19:** 13.

72 Plante DT. Sleep propensity in psychiatric hypersomnolence: a systematic review and meta-analysis of multiple sleep latency test findings. *Sleep Med Rev* 2017; **31:** 48–57.

73 Billiard M, Dolenc L, Aldaz C, Ondze B, Besset A. Hypersomnia associated with mood disorders: a new perspective. *J Psychosom Res* 1994; **38** (suppl 1): 41–47.

74 Nofzinger EA, Thase ME, Reynolds CF, et al. Hypersomnia in bipolar depression: a comparison with narcolepsy using the multiple sleep latency test. *Am J Psychiatry* 1991; **148:** 1177–81.

75 Kaplan KA, Harvey AG. Hypersomnia across mood disorders: a review and synthesis. *Sleep Med Rev* 2009; **13:** 275–85.

76 Cortese S, Konofal E, Yateman N, Mouren M-C, Lecendreux M. Sleep and alertness in children with attention-deficit/hyperactivity disorder: a systematic review of the literature. *Sleep* 2006; **29:** 504–11.

77 Lopez R, Micoulaud-Franchi J-A, Camodeca L, Gachet M, Jaussent I, Dauvilliers Y. Association of inattention, hyperactivity, and hypersomnolence in two clinic-based adult cohorts. *J Atten Disord* 2020; **24:** 555–64.

78 Zalai D, Bingeliene A, Shapiro C. Sleepiness in the elderly. *Sleep Med Clin* 2017; **12:** 429–41.

79 Dijk D-J, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 1994; **166:** 63–68.

80 Khalsa SBS, Conroy DA, Duffy JF, Czeisler CA, Dijk D-J. Sleep- and circadian-dependent modulation of REM density. *J Sleep Res* 2002; **11:** 53–59.

81 Hermann DM, Siccoli M, Brugger P, et al. Evolution of neurological, neuropsychological and sleep–wake disturbances after paramedian thalamic stroke. *Stroke* 2008; **39:** 62–68.

82 Saper CB, Fuller PM. Wake–sleep circuitry: an overview. *Curr Opin Neurobiol* 2017; **44:** 186–92.

83 Luppi P-H, Peyron C, Fort P. Not a single but multiple populations of GABAergic neurons control sleep. *Sleep Med Rev* 2017; **32:** 85–94.

84 Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 2000; **9:** 335–52.

85 Dauvilliers Y, Evangelista E, de Verbizier D, Barateau L, Peigneux P. [18F]Fludeoxyglucose-positron emission tomography evidence for cerebral hypermetabolism in the awake state in narcolepsy and idiopathic hypersomnia. *Front Neurol* 2017; **8:** 350.

86 Barateau L, Jaussent I, Roeser J, Ciardiello C, Kilduff TS, Dauvilliers Y. Cerebrospinal fluid monoamine levels in central disorders of hypersomnolence. *Sleep* 2021; **44:** zsab012.

87 Edgar DM. Circadian timekeeping in the squirrel monkey: neural and photic control of sleep, brain temperature, and drinking. PhD thesis, University of California, 1986: 360.

88 Edgar DM. Circadian control of sleep/wakefulness: implications in shift work and therapeutic strategies. In: Shiraki K, Sagawa S, Yousef MK, eds. Physiological basis of occupational health: stressful environments. Amsterdam: SPB Academic Publishing, 1996: 253–65.

89 Moradi A. Sleepiness and the risk of road traffic accidents: a systematic review and meta-analysis of previous studies. *Transp Res, Part F Traffic Psychol Behav* 2018; **65:** 620–29.

90 Sagaspe P, Taillard J, Bayon V, et al. Sleepiness, near-misses and driving accidents among a representative population of French drivers: sleepiness, near-misses and driving accidents in France. *J Sleep Res* 2010; **19:** 578–84.

91 Garbarino S, Durando P, Guglielmi O, et al. Sleep apnea, sleep debt and daytime sleepiness are independently associated with road accidents. a cross-sectional study on truck drivers. *PLoS One* 2016; **11:** e0166262.

92 Quera-Salva MA, Hartley S, Sauvagnac-Quera R, et al. Association between reported sleep need and sleepiness at the wheel: comparative study on French highways between 1996 and 2011. *BMJ Open* 2016; **6:** e012382.

93 Royant-Parola S, Kovess V, Brion A, Dagneaux S, Hartley S. Do hypnotics increase the risk of driving accidents or near miss accidents due to hypovigilance? The effects of sex, chronic sleepiness, sleep habits and sleep pathology. *PLoS One* 2020; **15:** e0236404.

94 Watson NF, Morgenthaler T, Chervin R, et al. Confronting drowsy driving: the American Academy of Sleep Medicine perspective: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med* 2015; **11:** 1335–36.

95 Ward KL, Hillman DR, James A, et al. Excessive daytime sleepiness increases the risk of motor vehicle crash in obstructive sleep apnea. *J Clin Sleep Med* 2013; **09:** 1013–21.

96 Quera Salva MA, Barbot F, Hartley S, et al. Sleep disorders, sleepiness, and near-miss accidents among long-distance highway drivers in the summertime. *Sleep Med* 2014; **15:** 23–26.

97 Burks SV, Anderson JE, Bombyk M, et al. Nonadherence with employer-mandated sleep apnea treatment and increased risk of serious truck crashes. *Sleep* 2016; **39:** 967–75.

98 Pizza F, Jaussent I, Lopez R, et al. Car crashes and central disorders of hypersomnolence: a French study. *PLoS One* 2015; **10:** e0129386.

99 Rocca FL, Finotti E, Pizza F, et al. Psychosocial profile and quality of life in children with type 1 narcolepsy: a case-control study. *Sleep* 2016; **39:** 1389–98.

100 Avis KT, Shen J, Weaver P, Schwebel DC. Psychosocial characteristics of children with central disorders of hypersomnolence versus matched healthy children. *J Clin Sleep Med* 2015; **11:** 1281–88.

101 Nakakubo S, Doi T, Makizako H, et al. Sleep duration and excessive daytime sleepiness are associated with incidence of disability in community-dwelling older adults. *J Am Med Dir Assoc* 2016; **17:** e1–5.

102 Alami YZ, Ghanim BT, Zyoud SH. Epworth Sleepiness Scale in medical residents: quality of sleep and its relationship to quality of life. *J Occup Med Toxicol* 2018; **13:** 21.

103 Stepnowsky C, Sarmiento KF, Bujanover S, Villa KF, Li VW, Flores NM. Comorbidities, health-related quality of life, and work productivity among people with obstructive sleep apnea with excessive sleepiness: findings from the 2016 US National Health and Wellness Survey. *J Clin Sleep Med* 2019; **15:** 235–43.

104 Léger D, Stepnowsky C. The economic and societal burden of excessive daytime sleepiness in patients with obstructive sleep apnea. *Sleep Med Rev* 2020; **51:** 101275.

105 Dauvilliers Y, Paquereau J, Bastuji H, Drouot X, Weil J-S, Viot-Blanc V. Psychological health in central hypersomnias: the French Harmony study. *J Neurol Neurosurg Psychiatry* 2009; **80:** 636–41.

106 Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019; **200:** 493–506.

107 Newman AB, Spiekerman CF, Md PE, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. *J Am Geriatr Soc* 2000; **48:** 115–23.

108 Gooneratne NS, Richards KC, Joffe M, et al. Sleep disordered breathing with excessive daytime sleepiness is a risk factor for mortality in older adults. *Sleep* 2011; **34:** 435–42.

109 Jaussent I, Bouyer J, Ancelin M-L, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep* 2011; **34:** 1103–10.

110 Blachier M, Dauvilliers Y, Jaussent I, et al. Excessive daytime sleepiness and vascular events: the Three City Study. *Ann Neurol* 2012; **71:** 661–67.

111 Empana J-P, Dauvilliers Y, Dartigues J-F, et al. Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the Three City Study. *Stroke* 2009; **40:** 1219–24.

112 Elwood P. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. *J Epidemiol Community Health* 2006; **60:** 69–73.

113 Qureshi AI, Giles WH, Croft JB, Bliwise DL. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. *Neurology* 1997; **48:** 904–11.

114 Jaussent I, Bouyer J, Ancelin M-L, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep* 2012; **35:** 1201–07.

115 Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. *Alzheimers Dement* 2019; **15:** 1039–47.

116 Benito-León J, Louis ED, Bermejo-Pareja F. Cognitive decline in short and long sleepers: a prospective population-based study (NEDICES). *J Psychiatr Res* 2013; **47:** 1998–2003.

117 Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013; **342:** 373–77.

118 Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol* 2014; **13:** 1017–28.

119 Peppard PE. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000; **284:** 3015.

120 Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. *J Otolaryngol Head Neck Surg* 2016; **45:** 43.

121 Bisogni V, Pengo MF, De Vito A, et al. Electrical stimulation for the treatment of obstructive sleep apnoea: a review of the evidence. *Expert Rev Respir Med* 2017; **11:** 711–20.

122 Roth T. Treating excessive daytime sleepiness in patients with narcolepsy. *J Clin Psychiatry* 2020; **81:** HB19045BR2C.

123 Pérez-Carbonell L. Treatment of excessive daytime sleepiness in patients with narcolepsy. *Curr Treat Options Neurol* 2019; **21:** 57.

124 Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. *Sleep* 2005; **28:** 667–72.

125 Bosco A, Lopez R, Barateau L, et al. Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy. *Neurology* 2018; **90:** e479–91.

126 Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev* 2012; **16:** 431–43.

127 Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, et al. Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. *Lancet Neurol* 2022; **21:** 53–65.

128 Kushida CA, Shapiro CM, Roth T, et al. Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy. *Sleep* 2022; **45:** zsab200.

129 Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol* 2013; **12:** 1068–75.

130 Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy: solriamfetol for ES/narcolepsy. *Ann Neurol* 2019; **85:** 359–70.

131 Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline and expert statements on the management of narcolepsy in adults and children. *Eur J Neurol* 2021; **28:** 2815–30.

132 Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2021; **17:** 1895–945.

133 Pépin JL, Georgiev O, Tiholov R, et al. Pitolisant for residual excessive daytime sleepiness in OSA patients adhering to CPAP: a randomized trial. *Chest* 2021; **159:** 1598–609.

134 Schweitzer PK, Rosenburg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial. *Am J Respir Crit Care Med* 2019; **199:** 1421–31.

135 Dauvilliers Y, Verbraecken J, Partinen M, et al. Pitolisant for daytime sleepiness in patients with obstructive sleep apnea who refuse continuous positive airway pressure treatment: a randomized trial. *Am J Respir Crit Care Med* 2020; **201:** 1135–45.

Copyright © 2022 Elsevier Ltd. All rights reserved.