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Excessive Daytime Sleepiness: A Clinical Review

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Abstract

Excessive daytime sleepiness (EDS) is a highly prevalent condition that is associated with significant morbidity. The causes of EDS are varied, and include inadequate sleep, sleep disordered breathing, circadian rhythm sleep-wake disorders, and central disorders of hypersomnolence (narcolepsy, idiopathic hypersomnia, and Kleine-Levin syndrome). Additionally, EDS could represent a symptom of an underlying medical or psychiatric disorder. Assessment of EDS includes a thorough sleep, medical, and psychiatric history, targeted clinical examination, and appropriate use of actigraphy to measure sleep duration and sleep-wake patterns, polysomnography to assess for associated conditions such as sleep-related breathing disorders or other factors that might disrupt nighttime sleep, multiple sleep latency testing to ascertain objective sleepiness and diagnose central disorders of hypersomnolence, and measurement of cerebrospinal fluid hypocretin-1 concentration. Treatment of EDS secondary to central disorders of hypersomnolence is primarily pharmacologic with wakefulness-promoting agents such as modafinil, stimulants such as methylphenidate and amphetamines, and newer agents specifically designed to improve wakefulness; behavioral interventions can provide a useful adjunct to pharmacologic treatment. When excessive sleepiness is secondary to other conditions, the treatment should focus on targeting the primary disorder. This review discusses current epidemiology, provides guidance on clinical assessments and testing, and discusses the latest treatment options. For this review, we collated the latest evidence using the search terms excessive sleepiness, hypersomnia, hypersomnolence, treatment from PubMed and MEDLINE and the latest practice parameters from the American Academy of Sleep Medicine.

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Excessive daytime sleepiness (EDS) is a major problem in the United States. Epidemiological studies have used varying definitions for excessive sleepiness, limiting our ability to compare prevalence across studies. Research using large general population samples have shown that up to 33% of US adults report excessive sleepiness during the daytime.[1] Excessive daytime sleepiness with associated symptoms of functional impairment has been found in 15.6% of the general adult population.[2] It can occur at any age, with one study finding that 41.5% of US adolescents reported feeling sleepy during the daytime.[3] Excessive daytime sleepiness is associated with a wide range of comorbidities, including sleep disorders, obesity, and psychiatric disorders.[4,5] Furthermore, EDS is associated with personal and occupational hazards that can impact public safety.[4,6-8]

Excessive daytime sleepiness, hypersomnolence, and hypersomnia are terms often used interchangeably; however, they carry different meanings that can vary depending on the classification system used.[9] Hypersomnolence refers to a symptom in the International Classification of Sleep Disorders-3, whereas hypersomnia is used in the names of specific sleep disorders.[10] In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, hypersomnia is used to refer to a symptom criterion, whereas a separate disorder with specific criteria is defined as hypersomnolence disorder. Hypersomnolence disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* is characterized by

excessive nighttime sleep, lapses into sleep during the day, and/or significant sleep inertia and is not related to narcolepsy, circadian rhythm sleep-wake disorders, or substance use.[11] In this article, we use the term excessive daytime sleepiness (EDS) as a symptom, and the term hypersomnia will be used to refer to specific disorders. Because of the varying definitions offered for hypersomnolence, we will avoid the use of that terminology. The objective of this review is to provide a general outline for assessment and management of EDS. We provide an overview of testing modalities, interpretation of the results, and current treatment options. For this review, we collated the latest evidence using the search terms excessive sleepiness, hypersomnia, hypersomnolence, treatment from PubMed and MEDLINE and the latest practice parameters from the American Academy of Sleep Medicine.

PRESENTATION

An individual struggling with EDS may complain of one or more of the following: feelings of excessive sleepiness; episodes of inadvertently falling asleep, including sleep attacks (episodes of falling asleep without prodromal symptoms of drowsiness); a prolonged main sleep episode that is unrefreshing; recurrent naps in the same day; and sleep inertia (prolonged difficulty waking up, with irritability, automatic behavior or confusion). Patients may complain of fatigue which will need to be differentiated from EDS as detailed below.

CONSEQUENCES OF EDS

Excessive daytime sleepiness is associated with both physical and mental comorbidities. Excessive daytime sleepiness contributes to motor vehicle accidents and fatalities each year.[7] One study of motor vehicle crashes in North Carolina between 1990 and 1992 attributed to a driver being asleep but not intoxicated reported a peak at night with a secondary peak during the mid-afternoon period of sleepiness and found a fatality rate similar to crashes attributed to alcohol use.[8] Excessive sleepiness in physicians and other health care providers has been shown to be associated with increased risk of medical errors.[12]

ARTICLE HIGHLIGHTS

- Excessive daytime sleepiness is a highly prevalent condition with significant morbidity.
- Excessive daytime sleepiness can result from insufficient sleep, primary sleep disorders such as sleep apnea or central disorders of hypersomnolence, or can be secondary to medication use, underlying medical or psychiatric illnesses.
- Evaluation of excessive daytime sleepiness involves taking a comprehensive history, conducting a focused exam, and using appropriate clinical testing.
- When excessive daytime sleepiness is secondary to other causes, they should be identified and treated.
- Central disorders of hypersomnolence require specialized pharmacological management.

Excessive daytime sleepiness is highly correlated with psychiatric comorbidity and functional limitation. Longitudinal studies have shown a strong association between depression and EDS.[4] Excessive daytime sleepiness in adults is associated with functional impairment and prior research has indicated an association between excessive sleepiness and significant impairment on the World Health Organization Disability Assessment Scale, a 30-day measure of function in self-care, mobility, cognition, social interaction, and role impairment.[1] In children, EDS is associated with parental report of depressive and anxious symptoms.[13] Adolescents who report constant daytime sleepiness are also likely to have a lower grade point average even when controlling for socioeconomic factors.[14] The relationship between EDS and psychiatric comorbidities is complex and may be bidirectional with respect to depression and anxiety.[15] In children, this bidirectionality may be seen in emotional and behavioral concerns, including attention-deficit/hyperactivity disorder, conduct issues, and problems with peers.[16-19]

COMMON CAUSES OF EXCESSIVE SLEEPINESS

Excessive daytime sleepiness is most commonly a result of insufficient sleep.[20] A

cross-sectional study of truck drivers found a mean average sleep duration of 5.6 hours, and 46% of truckers in the study reported hypersomnia.[21] The American Academy of Sleep Medicine (AASM) recommends adults 18 to 60 years old obtain at least 7 hours per night of sleep.[22] A significant proportion of adults in the United States do not get the recommended amount of sleep: the 2014 Centers for Disease Control Behavioral Risk Factor Surveillance System Survey revealed that up to one-third of respondents obtained less than 7 hours of sleep per night.[23] Shift work is an important contributor to insufficient sleep and circadian misalignment, both contributing to EDS.[24] Similarly, insufficient sleep is common in adolescents, and should be a major consideration while evaluating adolescents presenting with EDS; one survey identified 45.7% of adolescents reporting EDS occurring more than once per week.[14]

Physical comorbidities are also associated with incident daytime sleepiness. A longitudinal study of individuals from the Penn State Adult Cohort found a significant association between obesity and weight gain, and onset and persistence of EDS. This study also found an association between sleep apnea, diabetes mellitus, and incident EDS.[4] Besides sleep apnea, other breathing disorders such as asthma as well as gastroesophageal reflux disease can disrupt nighttime sleep and lead to daytime sleepiness.[25,26] Likewise, several psychiatric comorbidities are associated with EDS; in particular, mood disorders such as depression and bipolar disorder.[9] The presence of EDS in subjects with these disorders can moderate treatment effect and increase the risk of relapse to a mood episode.[27]

Among sleep disorders, obstructive sleep apnea (OSA) is often associated with EDS. Repeated nighttime awakenings, obesity, hypercapnia, and tissue damage in the sleep-wake brain regions secondary to hypoxia occurring in the context of OSA may potentially result in EDS. In addition, circadian rhythm sleep-wake disorders such as delayed sleep-wake phase disorder or jet lag disorder which result from a misalignment between the body clock and social requirements can present with EDS, especially when the patient needs to be awake but their alertness level secondary to their internal body clock is at its nadir. These circadian rhythm sleep-wake disorders can also lead to insufficient sleep.

Central disorders of hypersomnolence are characterized by excessive sleepiness not attributable to disturbed nocturnal sleep or circadian misalignment, and are often caused by primary central nervous system abnormalities.[10] These include narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, and Kleine-Levin syndrome.

Narcolepsy is characterized clinically by severe EDS. Cataplexy, present in about two-thirds to three-quarters of patients, is highly specific for the diagnosis.[28] Hypnagogic hallucinations, hypnopompic hallucinations, and sleep paralysis may be present; similar to cataplexy, these symptoms also result from rapid eye movement (REM) intrusion into wakefulness, but are less specific phenomena. Cataplexy is characteristic of narcolepsy type 1, and consists of a loss of muscle tone in the face, neck, or legs triggered most frequently by sudden positive emotions, usually related to mirth, or at times by anger or being startled. Patients with narcolepsy type 2 do not have cataplexy. Although hypnagogic and hypnopompic hallucinations can occur in any sensory modality, they are usually visual in nature. These patients can occasionally present with automatic behaviors secondary to short microsleep episodes during the daytime.[29]

Most patients with narcolepsy are thought to have an autoimmune disorder.[30] The pathologic basis for narcolepsy type 1 is loss of hypocretin-1 (also known as orexin-A) synthesizing neurons in the hypothalamus. This can be diagnosed clinically by measuring cerebrospinal fluid (CSF) hypocretin-1 levels or, more commonly, using a surrogate marker of a combination of cataplexy and short latencies to REM sleep on a multiple sleep latency test (MSLT). However, approximately 24% of patients with narcolepsy without cataplexy have low or absent CSF hypocretin-1, if the value

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has been determined, and are included under narcolepsy type 1.[31] Narcolepsy type 2 is also characterized by short latencies to REM sleep, but patients do not have cataplexy. If tested, CSF hypocretin-1 levels should be normal. The pathogenesis of narcolepsy type 2 is uncertain.

Idiopathic hypersomnia is also characterized by EDS, but without cataplexy, and without REM sleep intrusions.[32] The most typical phenotype consists of prolonged nocturnal sleep episodes that are unrefreshing, severe sleep inertia, and daytime naps that are typically long and unrefreshing. Other patients with a less specific phenotype resemble patients with narcolepsy type 2 apart from the absence of premature REM sleep. It has been recently suggested that these two groups should be classified together as "narcolepsy spectrum disorder," but this terminology has not been incorporated into any formal nosologies as yet.[33]

Kleine-Levin syndrome is a rare sleep disorder, generally occurring in adolescent males, characterized by relapsing-remitting periods of excessive sleepiness, cognitive impairment, altered perception, eating disorder (hyperphagia or anorexia), depressed mood, and disinhibited behavior, including hypersexuality. Episodes may last from 2 days to 5 weeks and occur at least once every 18 months, with periods of normal cognition and sleepiness in between episodes. The disorder often spontaneously resolves by 30 years of age.[34]

The differential diagnosis of EDS is detailed in Table 1.

ASSESSMENT

History

Assessment of EDS should begin with obtaining a thorough patient history. The sleep history should include information regarding bed and wake times on weekdays and weekends, total daily sleep time, sleep habits, and daytime routines. The patient's stated preference for time to bed and time to wake may help uncover a circadian rhythm sleep-wake disorder. A history of loud snoring, witnessed pauses in respiration, and nighttime choking episodes suggest a high likelihood of OSA. The presence of cataplexy suggests narcolepsy. Other nighttime symptoms that may be associated with daytime sleepiness include symptoms suggestive of restless legs syndrome, characterized by periods of insomnia associated with an urge to move the legs relieved by movement. Restless legs syndrome is usually associated with periodic leg movements of sleep, but these movements are common, especially in older persons. Very occasionally, periodic leg movements of sleep may cause EDS without accompanying restless legs syndrome, a condition known as periodic limb movement disorder. Additional history should assess for symptoms suggestive of depression, gastrointestinal reflux, pain, or respiratory conditions, and a history of allergies or asthma which can lead to nighttime sleep disruption resulting in daytime sleepiness.[35] Collateral history from a bed partner can be useful to identify symptoms suggestive of OSA or periodic limb movements and should be obtained whenever possible.

A thorough medication and substance use history is important in the assessment of EDS. Over-the-counter medications that can cause sedation include antihistamines and nonprescription sleeping pills. A number of prescription medications can result in increased sedation. These commonly include alpha-2-agonists, benzodiazepines, prescription sleep medications, dopamine agonists, anticonvulsants, opioids, and other psychotropic medications such as antipsychotics and some antidepressants. Substances of abuse may also cause daytime sleepiness. Alcohol is the most widely used sedative substance, but marijuana and opioids may also result in daytime sedation.[36] Additionally, benzodiazepines and other sedative/hypnotics may also be misused/abused resulting in daytime sleepiness. The clinician should also be vigilant about the possibility of substance withdrawal from cocaine and other stimulants including caffeine that can present with excessive sleepiness.[37]

It is important to distinguish between sleepiness and fatigue. The distinction between the two terms, as used in sleep medicine, should be explained to the patient.

TABLE 1. Differential Diagnosis of Excessive Sleepiness

Central disorders of hypersomnolence
Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnia
Kleine-Levin syndrome
Sleep-related breathing disorders
Obstructive sleep apnea
Central sleep apnea
Circadian rhythm sleep-wake disorder
Delayed sleep-wake phase disorder
Advanced sleep-wake phase disorder
Irregular sleep-wake rhythm disorder
Non—24 hour sleep-wake rhythm disorder
Shift work sleep disorder
Jet lag disorder
Circadian rhythm sleep-wake disorder not otherwise specified
Secondary to another cause
Excessive sleepiness secondary to a medical disorder (Parkinson disease, traumatic brain injury, infections, hypothyroidism, etc)
Excessive sleepiness secondary to a psychiatric disorder (atypical depression or bipolar disorder type II)
Excessive sleepiness secondary to a medication (benzodiazepines, opiates, alcohol, etc)
Insufficient sleep syndrome

From Sateia et al.[10]

Fatigue is a lack of energy with a reduced ability to perform physical activities that would have previously been easily accomplished. It may be accompanied by mental fatigue with poor concentration and memory, but it is not generally associated with inappropriate episodes of sleep during the day. Although occasionally fatigue may be caused by OSA, it is generally associated with chronic medical, neurological, or psychiatric conditions, or occurs in isolation as in chronic fatigue syndrome. In contrast, the presence of environmental or intrinsic sleep disorders should be sought in patients who clearly have EDS. Women with OSA are more likely to report fatigue rather than sleepiness as their main symptom.[38]

Measurement Scales

Measurement scales are a useful complement to history-taking and sleep logs. Although a number of scales exist, three are commonly used: Epworth sleepiness scale, Stanford sleepiness scale and the Karolinska sleepiness scale.[39-41]

The Epworth sleepiness scale is an eight-item measure designed to assess overall sleepiness, and asks the patient to rate their likelihood of falling asleep in different scenarios, on a scale of 0 to 3.[39] By consensus, a score of 11 or greater is thought to indicate excessive sleepiness.

The Stanford sleepiness scale is a seven-point scale ranging from very alert to very sleepy at a given point in time.[42] The Karolinska sleepiness scale is a nine-point scale ranging from extremely alert to extremely sleepy, designed to measure the 10-minute period immediately before administering the scale.[43] Because the Stanford and Karolinska sleepiness scales measure momentary sleep, they may be more useful to assess sleep during a specific period and are commonly used in research studies, whereas the Epworth sleepiness scale may be helpful for a general understanding of a patient's level of sleepiness, and thus has greater clinical application.[44]

Physical Examination

Physical examination for assessment of excessive sleepiness should include evaluation for findings that are present in disorders commonly associated with this symptom and include a description of the level of alertness during the exam.

An elevated body mass index and increased neck circumference are risk factors for OSA. A crowded oropharynx with erythematous pharyngeal walls can also be suggestive of a high risk of OSA. Other physical abnormalities may include midface hypoplasia, micrognathia, retrognathia, enlarged tonsils, or a deviated nasal septum. It is also important to assess for signs of insulin resistance, such as acanthosis nigricans as well as for signs of acromegaly and hypothyroidism, which can suggest an increased risk of OSA.[35]

Physical examination findings in those with circadian rhythm sleep-wake disorders, narcolepsy, or idiopathic hypersomnia are usually normal; although examination during a cataplectic attack reveals hypotonia, areflexia, and sometimes facial twitching. Cataplexy is rarely observed in the clinic, but

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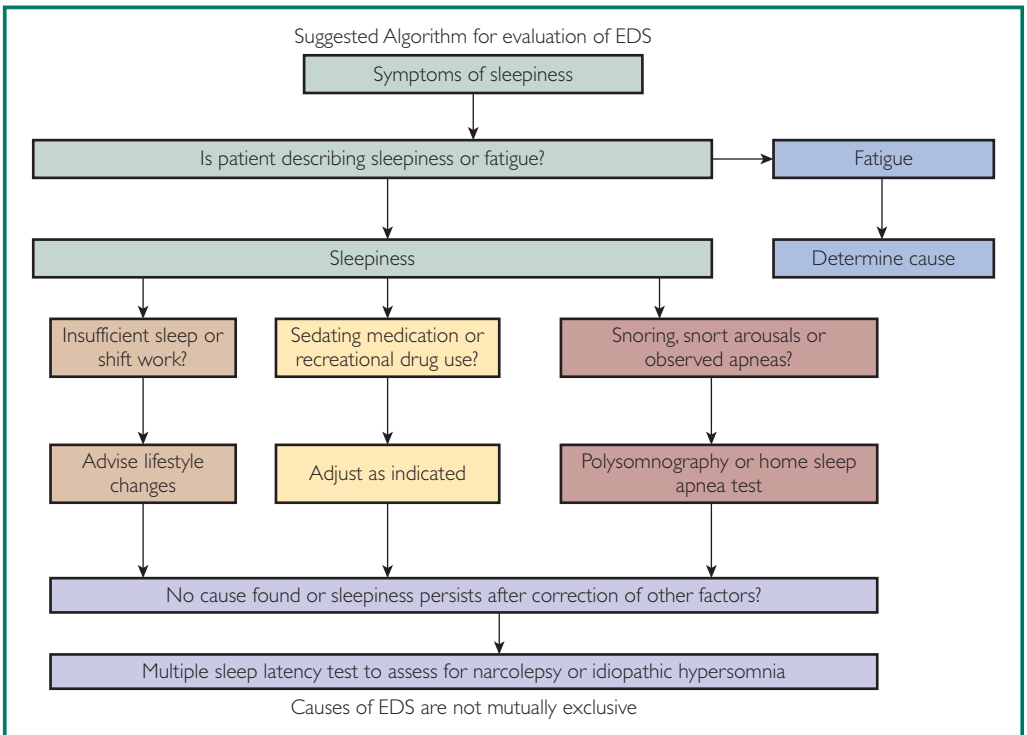

FIGURE 1. Algorithm for the assessment and treatment of excessive daytime sleepiness.

when it occurs, clinicians should test deep tendon reflexes as their transient absence is highly specific for the disorder.[45,46] In patients with suspected central disorders of hypersomnolence, a neurological examination should be performed to assess for the presence of a neurological disorder affecting the brainstem, thalamus, or hypothalamus.

Testing

An algorithm for the investigation of EDS is shown in Figure 1. Many factors contributing to EDS can be elucidated by primary care practitioners, but when a central disorder of hypersomnolence is suspected or the cause is uncertain, a referral to a sleep specialist for testing is indicated. Obstructive sleep apnea can often be diagnosed by home sleep apnea tests, but treatment of sleep-disordered breathing usually requires involvement of a sleep specialist.

Testing in the assessment of EDS consists of three major modalities: actigraphy, polysomnography (PSG), and MSLT. Objective measures of EDS include prolonged sleep durations as measured by wrist actigraphy or continuous PSG, and a shortened mean sleep latency (MSL) measured by the MSLT.[47]

Actigraphy, a relatively inexpensive and noninvasive technique that provides a surrogate marker of sleep and wakefulness, can be particularly useful for identifying insufficient sleep and circadian rhythm sleep-wake disorders.[48] Actigraphs are wristwatch-like devices that measure movement, which serves as a surrogate for wakefulness. These can be used by the patient in their home over several days to weeks, and can be a useful supplement to a sleep log.[9,35] However, sleep logs may overestimate total sleep, and actigraphy may underestimate wake time and overestimate sleep time during the day.[9,49,50] These limitations should be taken into consideration during the interpretation of these measures. Average daily sleep times of at least 660 minutes in adults can help identify a diagnosis of idiopathic hypersomnia.[10]

Polysomnography quantifies sleep and breathing abnormalities. It consists of nighttime monitoring in a sleep laboratory, with sensors that provide information on

electroencephalography, electrooculography, breathing parameters (including airflow, breathing effort, snoring, and pulse oximetry), body position, electrocardiography, and electromyography. This can help detect sleep-disordered breathing, periodic limb movements, and other causes of nighttime sleep disruption which can result in daytime sleepiness. Rapid eye movement sleep occurring within 15 minutes of sleep onset on PSG is strongly suggestive of a diagnosis of narcolepsy and counts towards the number of sleep-onset REM episodes (SOREMs) necessary in making a diagnosis of narcolepsy.[51]

The gold standard for the objective assessment of EDS is the MSLT, which involves providing patients with four to five nap opportunities at 2-hour intervals following their awakening, and measures their propensity to fall asleep. It is designed to objectively quantify sleepiness under standardized conditions and detect the presence of SOREMs. For the test to be a valid diagnostic method for the diagnosis of central disorders of hypersomnolence, careful attention must be paid to avoiding prior sleep deprivation and the discontinuation of all psychotropic medication likely to impact sleep propensity and influence REM sleep at least 2 weeks or 5 half-lives before the study. Performing the test while the patient is taking antidepressants or other medications that can affect sleep latency or REM latency results in uninterpretable results; thus, the MSLT should not be used if it is unsafe to discontinue these medications. To ensure adequate sleep before the MSLT, actigraphy and sleep logs are used for 1 to 2 weeks preceding testing and PSG performed the night before the conduct of the MSLT to ensure adequate sleep before the MSLT and rule out other potential causes of EDS sleepiness as listed above. Patients are also advised to discontinue the use of illicit drugs that might impact sleep/wakefulness and supplements or over-the-counter medication such as melatonin and diphenhydramine. Urine drug testing may be indicated to ensure that excessive sleepiness on the MSLT is not pharmacologically induced.

An MSL on an MSLT of less than 5 minutes is considered indicative of objective sleepiness, whereas a value greater than 10 minutes is considered normal. Between these values there is overlap between normal and abnormal, and clinical judgment should be used in interpreting the results. Although an MSL of 8 minutes is cited by the International Classification of Sleep Disorders-3 as a cutoff value, this should be used with caution in the clinical context.[10]

The presence of two or more SOREMs (including a SOREM that has occurred on the PSG before the MSLT) is considered abnormal. As long as other causes, such as insufficient sleep, shift work, moderate or severe OSA, or cessation of the use of REM suppressant medications less than 2 weeks before the test, have been excluded, this in conjunction with a short MSL (usually defined as $\leq$8 minutes), is indicative of a diagnosis of narcolepsy.[5] An MSL of less than or equal to 8 minutes with fewer than 2 SOREMs supports a diagnosis of idiopathic hypersomnia (Table 2).

However, some patients with the classic phenotype of idiopathic hypersomnia may have normal MSL on an MSLT. An alternative criterion for the diagnosis is a total daily sleep time of at least 660 minutes. Various polysomnographic protocols have been proposed, including multi-day studies, but these are rarely performed in the United States.[52] Wrist actigraphy for 1 week with the patient allowed to sleep whenever desired is a more practical method of assessing this parameter.

Human Leukocyte Antigen and CSF Hypocretin-1 Tests

Studies have identified DQB1*06:02, an HLA antigen, as being associated with narcolepsy. DQB1*06:02 is found in 90% to 95% of African American, White, and Japanese patients with narcolepsy type 1, and it 45% to 50% of patients with narcolepsy type 2. However, approximately 25% of the general population may have this gene, significantly limiting its specificity in clinical practice.[31]

To help make a diagnosis of narcolepsy, CSF hypocretin-1 levels may be measured. In narcolepsy type 1, CSF hypocretin-1 concentration, measured by immunoreactivity, is either less than or equal to 110 pg/mL or

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TABLE 2. Multiple Sleep Latency Test and Polysomnography Findings for Specific Disorders[a]

Disorder	Laboratory findings
Narcolepsy type 1	MSLT mean sleep latency ≤8 minutes At least two sleep-onset rapid eye movement periods on MSLT and PSG Cataplexy present Or CSF hypocretin-1 concentration ≤110 pg/mL or <one-third of mean values obtained in normal subjects with the same standardized assay
Narcolepsy type 2	Mean sleep latency ≤8 minutes <2 sleep-onset rapid eye movement periods on MSLT and PSG No cataplexy present CSF hypocretin-1 concentration (if measured) >110 pg/mL or > one-third of mean values obtained in normal subjects with the same standardized assay
Idiopathic hypersomnia	Mean sleep latency ≤8 minutes <2 sleep-onset rapid eye movement periods (on MSLT and PSG) No cataplexy present CSF hypocretin-1 concentration (if measured) >110 pg/mL or > one-third of mean values obtained in normal subjects with the same standardized assay Or Total 24-hour sleep time ≥660 minutes on 24-hour PSG monitoring or 7-day actigraphic recording with unrestricted sleep

[a]CS = cerebrospinal fluid; MSLT = multiple sleep latency test; PSG = polysomnogram.

less than one-third of mean values obtained in healthy subjects with the same standardized assay. Indications for this test include suspected narcolepsy when it is not possible to perform a valid MSLT, such as the need for patients to remain on psychotropic medications, untreated OSA, insufficient sleep or shiftwork, or in children 5 years of age or younger. Human leukocyte antigen testing should always be performed first, as essentially all patients with low CSF hypocretin-1 levels and narcolepsy will have the DQB1*06:02 antigen. It is important to understand that patients with narcolepsy type 2 and idiopathic hypersomnia have normal hypocretin-1 levels; therefore, a normal value does not rule out these disorders. The test may also be helpful in selected patients with EDS associated with neurodegenerative disorders or autoimmune encephalopathies, and in distinguishing cataplexy from functional disorders. The test is currently only performed in a few national centers in the United States.

TREATMENT

When EDS is secondary to other causes, these should be identified and treated first. A treatment algorithm for the management of EDS is shown in Figure 2. Clinicians should be aware that there are no head-to-head trials showing superiority of a single agent and this algorithm is developed balancing the current evidence base, abuse potential of the drugs, and side-effect profiles. Clinicians should also incorporate patient preference and cost implications while choosing an appropriate agent.

Nonpharmacologic

Nonpharmacologic and behavioral treatments are helpful as adjunctive options in the treatment of EDS. The most important aspect of behavioral management of EDS is ensuring that the patient obtains a sufficient amount of sleep.

Additional modalities may include scheduled naps, distraction, exercise, sleep hygiene measures, and behavioral therapy.[9] Scheduled naps can be a helpful adjunct in treatment of narcolepsy, but are rarely sufficient alone in the treatment of the disorder.[53] Distraction techniques such as chewing gum have been shown to have a moderate degree of utility in promoting wakefulness.[54] Physical activity has been

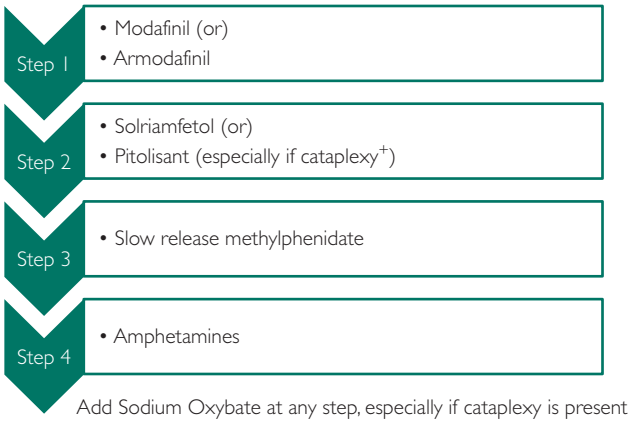

FIGURE 2. Suggested algorithm for management of narcolepsy.

shown to improve wakefulness in animal models of narcolepsy.[55] Another important nonpharmacological approach to consider in patients with OSA and EDS is improving adherence to continuous positive airway pressure. In patients with OSA, continuous positive airway pressure has been shown to reduce daytime sleepiness. Prior literature suggests that whereas greater than or equal to 4 hours of use can result in subjective improvements, at least 6 hours of use are required to result in improvements in objective measures of sleepiness.[56]

Medications

Pharmacologic treatment of EDS includes both US Food and Drug Administration (FDA)—approved and off-label medications, and may target either the underlying cause or the symptom of excessive sleepiness. For the treatment of EDS in narcolepsy, modafinil, armodafinil, dextroamphetamine, mixed amphetamine/dextroamphetamine, methylphenidate, sodium oxybate, solriamfetol, and pitolisant are FDA-approved.[53] There are no FDA-approved treatments of idiopathic hypersomnia. Table 3 contains a summary of medications used for central disorders of hypersomnolence, usual dosing regimens, and common side effects.

Methylphenidate and Amphetamines. Dextroa mphetamine, methylphenidate, and mixed amphetamine/dextroamphetamine are FDA approved for the treatment of narcolepsy. However, methylphenidate and many amphetamine preparations are used for the management of idiopathic hypersomnia, and are included as a treatment option in the AASM practice parameters.[53,71] The methylphenidate class mainly inhibits catecholamine reuptake, whereas the amphetamine class elevates extracellular dopamine by multiple mechanisms.[57] Dosing is generally titrated to effect, with a maximal recommended dose of 100 mg daily for both the amphetamine and methylphenidate classes of medication.[71] Slow release preparations are preferred to avoid peak and trough effects of short-acting drugs.

Common considerations while initiating these medications include increases in the pulse rate and blood pressure; appetite suppression with weight loss can also occur. An electrocardiogram should be obtained before use of amphetamines as these drugs can increase the QT_C interval. Studies that have examined their use in sleep-specific populations have also shown an increased risk of psychosis and anorexia, especially in supratherapeutic doses.[59] These medications are currently US Drug Enforcement Agency Schedule II controlled substances, indicating a moderate risk of abuse. Some patients will develop tolerance to the stimulant effects but there is no evidence that drug holidays prevent this.

Modafinil and Armodafinil. Modafinil and armodafinil are FDA-approved for the treatment of EDS from narcolepsy, sleepiness persisting after adequate treatment of OSA, and shift-work disorder. They are also included as a treatment option for idiopathic hypersomnia in the AASM practice parameters.[53] Armodafinil is the R-enantiomer of modafinil, with serum concentrations persisting slightly longer after a dose, but this difference is rarely clinically significant. Their mechanism of action is uncertain. Modafinil is generally prescribed initially as 200 mg in the morning, and armodafinil as 150 mg in the morning, but many patients require higher or twice daily doses.[60,62]

Side effects are uncommon with these medications, but a potentially serious effect

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TABLE 3. Medications for Excessive Daytime Sleepiness[a]

Drug name	Mechanism of action	Indications	Dosage	Common side effects	Contraindications and Precautions
Methylphenidate and amphetamines	Catecholamine induction (amphetamine class)[57]; catecholamine reuptake inhibition (methylphenidate class)[58]	Narcolepsy (methylphenidate), idiopathic hypersomnia (off-label),	Max recommended dose 100 mg daily[59]	Appetite suppression and weight loss, nausea, anxiety, headache, increased heart rate and blood pressure, skin-picking behaviors	Risk of psychosis in high doses, substance misuse/abuse history, cardiac disease, uncontrolled hypertension; amphetamines prolong QTc
Modafinil	Uncertain[60]	Narcolepsy, residual sleepiness after adequately treated OSA, shift work sleep disorder, idiopathic hypersomnia (off-label)	200-400 mg once or twice daily/before shift	Headache, nausea, anorexia, Stevens-Johnson syndrome	Known hypersensitivity to modafinil or armodafinil[61]; interaction with oral contraceptives
Armodafinil	Uncertain[62]	Narcolepsy, residual sleepiness after adequately treated OSA, shift work sleep disorder, idiopathic hypersomnia (off-label)	150-250 mg in the morning or twice daily/before shift	Headache, nausea, anorexia, Stevens-Johnson syndrome	Known hypersensitivity to armodafinil or modafinil[62]; interaction with oral contraceptives
Solriamfetol	Dopamine/norepinephrine reuptake inhibitor[63]	Narcolepsy, residual sleepiness after adequately treated OSA, idiopathic hypersomnia (off-label)	Up to 150 mg daily, starting at 75 mg (narcolepsy) or 37.5 mg daily (OSA)	Headache, nausea, decreased appetite, increased heart rate, anxiety	Uncontrolled hypertension/ other cardiac disease[64]; monoamine oxidase inhibitors
Pitolisant	Selective H3 receptor antagonist/ inverse agonist[65]	Narcolepsy (hypersomnolence and cataplexy), idiopathic hypersomnia (off-label)	17.8-35.6 mg daily, starting dose 8.9 mg	Insomnia, nausea, anxiety	Severe hepatic impairment[66]; interacts with oral contraceptives; prolongs QTc interval
Sodium oxybate	$GABA_B$ receptor agonist[67]; mechanism uncertain	Narcolepsy, (hypersomnolence and cataplexy)	6-9 grams per night (in divided doses timed 2-4 hours apart)	Nausea, sedation, weight loss, sleep walking, nocturnal enuresis	Substance misuse/abuse history, use with sedatives or alcohol, untreated OSA, moderate to severe lung disease, hypoventilation[68], succinic semialdehyde dehydrogenase deficiency[69]
Lithium	Unknown[70]	Kleine-Levin Syndrome (off-label)	Starting dose around 300 mg 3 times daily, titrate to effect or around 0.8-1.2 mEq/mL[34]	Hand tremor, polyuria, thirst, nausea, discomfort	Renal disease, thyroid disease, parathyroid disease

[a]OSA = obstructive sleep apnea.

of Stevens-Johnson syndrome could occur in rare instances. Other possible side effects include headache, nausea, dry mouth, and anorexia. The drugs are cytochrome P3A4 inducers and may lower the concentration of oral contraceptives; all women of childbearing age should be warned that alternative contraceptive measures may be needed. Long-term studies have shown moderate efficacy in narcolepsy. Both modafinil and armodafinil are schedule IV controlled substances, indicating possible but low potential for abuse.

Solriamfetol. Solriamfetol is FDA-approved for the treatment of EDS in narcolepsy and sleepiness persisting in adequately treated OSA. It is the only dopamine/norepinephrine reuptake inhibitor approved for the treatment of a disorder of hypersomnolence. Dosing starts at 37.5 mg daily for OSA or 75 mg daily for narcolepsy, and can be titrated to a maximal recommended dose of 150 mg daily.[64] The most common side effects include headache, nausea, decreased appetite, increased heart rate and anxiety, and are dose-dependent. It should not be used with monoamine oxidase inhibitors. If used in combination with serotonin and norepinephrine reuptake inhibitors such as venlafaxine, monitoring for sympathomimetic side effects is advisable. Solriamfetol is currently a schedule IV drug.

Pitolisant. Pitolisant is a newly FDA-approved treatment of EDS in narcolepsy and also decreases the frequency of cataplexy. It is unique in its mechanism of action compared with the other medications discussed in that it acts as a histamine H3 receptor antagonist/inverse agonist.[65] Its action is mediated at the presynaptic level and leads to activation of histaminergic neurons. Pitolisant also modulates the release of other wakefulness promoting neurotransmitters such as dopamine, noradrenaline, and acetylcholine. This medication is titrated up from a starting dose of 8.9 mg to a maximal dose of 35.6 mg daily.[66] The most common side effects reported include headache, nausea, and anxiety. An electrocardiogram should be performed before use as the drug can increase the QTc interval. It may decrease the efficacy of oral contraceptives. Serum levels of the medication may be increased by concomitant use of selective serotonin reuptake inhibitors and tricyclic antidepressants may reduce its therapeutic effect. Pitolisant is not scheduled under the controlled substances act.

Sodium Oxybate. Sodium oxybate is a first-line treatment for cataplexy and also improves EDS, especially when used in combination with modafinil.[72] It is a $GABA_B$ receptor agonist, but the specific mechanism by which sodium oxybate exerts its effects in narcolepsy is uncertain.[73] The drug is taken in two divided doses before sleep and 2 to 4 hours later. The total daily dose is 6 to 9 g.[72] Side effects associated with the use of sodium oxybate include sedation, nausea, weight loss, nocturnal enuresis, and sleep walking. It is a respiratory depressant and should never be combined with alcohol or hypnotics, or used in patients with untreated OSA, moderate to severe lung disease, or other causes of hypoventilation. It is a schedule I controlled substance that requires special registration for providers and is dispensed through a single pharmacy in the United States.

Other. There are limited treatments available for Kleine-Levin syndrome. Evidence suggests that lithium, generally titrated to a blood level in the upper range for treatment of mania (ie, around 0.8 to 1.2 mEq/mL), may decrease the frequency and duration of episodes of Kleine-Levin syndrome.[74] Other antiepileptic mood stabilizers have also been studied for the treatment of Kleine-Levin syndrome but appear to be less efficacious.[34] Amantadine may be beneficial in improving sleepiness during an episode in some patients.[75]

An important consideration for treatment is the abuse potential with a number of these agents, particularly methylphenidate, amphetamines, and sodium oxybate. For stimulants such as methylphenidate and amphetamines,

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the data suggest that dosage within recommended guidelines may be relatively safe from an abuse potential standpoint: a retrospective study of 105 patients diagnosed with narcolepsy or idiopathic hypersomnia (11% of whom had a history of illicit substance misuse) found that no patients misused their prescribed stimulant.[76] However, a retrospective case-control study of patients receiving high-dose stimulants (above the maximum recommended dose) did find an odds ratio of 4.3 of the presence of alcohol or polysubstance misuse. Although a history of substance use disorder should not be a contraindication for treatment of central disorders of hypersomnolence, the clinician may wish to consider treatment options with a lower abuse potential, such as pitolisant. A majority of the medications used to treat EDS have been shown to have teratogenic effects in animal studies and there are no detailed practice parameters on treatment during pregnancy. The decision about whether to discontinue medications in pregnancy should be based on shared decision-making principles after weighing risks and benefits and are reviewed in detail elsewhere.[77]

Treatment of EDS secondary to medical conditions varies, and evidence is often limited by small numbers of patients being treated. The AASM practice parameters list modafinil as a treatment option for EDS due to Parkinson disease, myotonic dystrophy, and multiple sclerosis. A small study suggests that methylphenidate may be effective for the treatment of EDS secondary to myotonic dystrophy.[53]

CONCLUSION

Excessive daytime sleepiness is a potentially hazardous condition with varied etiologies, warranting thorough assessment and treatment. Assessment begins with a comprehensive history and delineation of sleep patterns with an emphasis on inadequate sleep, ruling out circadian rhythm sleep-wake disorders, OSA, and the presence of medical and psychiatric comorbidities. Evaluation of excessive sleepiness should include targeted tests conducted under ideal circumstances to avoid spurious results. Medications are the mainstay of the treatment for central disorders of hypersomnolence and behavioral interventions may play a useful adjunctive role.

Abbreviations and Acronyms: **AASM** = American Academy of Sleep Medicine; **CSF** = cerebrospinal fluid; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; **EDS** = excessive daytime sleepiness; **FDA** = US Food and Drug Administration; **MSL** = mean sleep latency; **MSLT** = multiple sleep latency test; **OSA** = obstructive sleep apnea; **PSG** = polysomnogram; **REM** = rapid eye movement; **SOREM** = sleep-onset rapid eye movement episode

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Update

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CORRECTION

Correction to 'Excessive Daytime Sleepiness: A Clinical Review' [*Mayo Clinic Proceedings* 96 (2021) 1288–1301/3097]

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From the Department of Psychiatry and Psychology (K.D.G., B.P.K.), Center for Sleep Medicine (M.P.M., M.H.S., B.P.K.), and the Department of Neurology (M.H.S.), Mayo Clinic, Rochester, MN.

In the article "Excessive Daytime Sleepiness: A Clinical Review—Clarification on the Scheduling of Sodium Oxybate," by Kriti D. Gandhi, Meghna P. Mansukhani, Michael H. Silber, and Bhanu Prakash Kolla (*Mayo Clin Proc* 2021; 96(5): 1288–1301, the authors would like to make a clarification: The active ingredient of Sodium Oxybate Oral Solution, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance per the DEA. However, the prescription form- Sodium Oxybate Oral Solution (Xyrem and Xywav) are separately classified as Schedule III controlled substances which should be used in conjunction with the REMS program.

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