Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea:

Disease State and Treatment Overview

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EXCESSIVE DAYTIME SLEEPINESS

The American Academy of Sleep Medicine (AASM) defines excessive daytime sleepiness (EDS) as the inability to maintain wakefulness and alertness during normal major waking episodes of the day, resulting in the irrepressible need for sleep or unintended lapses into drowsiness or sleep.[1,2] A variety of conditions can cause EDS, including insufficient sleep, shift work, medications or illicit drugs, or it can occur secondary to medical or psychiatric disorders (eg, Parkinson's disease, multiple sclerosis, or chronic renal insufficiency).[1,3] Irrespective of the cause, EDS can lead to unwanted sequelae, including impairments in health, work performance and social functioning, and potential danger when driving.[1,4]

It is important to distinguish fatigue, a common complaint, from EDS. Fatigue is a mental or physical feeling of exhaustion or reduced energy that is associated with many chronic medical and psychiatric disorders. Fatigued people may not actually be sleepy, suggesting a different etiology from other disorders that cause EDS.[5] EDS is characterized by an increased need to sleep during the day that can vary in severity and is most likely to occur when the person is sedentary, bored, or in a monotonous situation requiring little to no active participation.[1]

DISORDERS ASSOCIATED WITH EDS

There are many causes of EDS, and there may be multiple contributing factors in any one patient. Some of the most common causes of EDS are insufficient sleep, medications, and medical and psychiatric disorders. Examples of conditions leading to EDS include sleep-related breathing disorders (obstructive sleep apnea [OSA]), central disorders of hypersomnolence (narcolepsy types 1 and 2, idiopathic hypersomnia), and circadian rhythm sleep-wake disorders (non–24 hour sleep-wake rhythm disorder, shift work disorders, jet lag).[1,2] Table 1 outlines some of the major medical/psychiatric and sleep-related disorders that can lead to EDS.[2,3,6] This discussion will focus mainly on OSA with EDS, but it is important to note the variety of potential causes of EDS.

EDS can occur secondary to medical and psychiatric disorders. Endocrine abnormalities (diabetes mellitus, hypothyroidism) and infectious diseases (HIV, central nervous system Lyme disease), alcohol, drugs (illicit or otherwise), neurologic (head trauma), and psychiatric disorders (depression) can cause excessive sleepiness.[3] Furthermore, EDS is prevalent in Parkinson's disease and can have a substantial impact on patients' daily lives.[6]

EDS can be caused by circadian rhythm disorders.[7] Shift work disorder is of clinical relevance because shift workers comprise about 15% of the full-time workforce.[7,8] Night shift workers, particularly those who drive at night, are at the greatest risk for chronic sleep loss, and the National Safety Council has determined that the risk of safety incidents is 30% greater during the night shift compared with the morning shift.[8]

EDS is a cardinal feature of narcolepsy and all patients with narcolepsy experience EDS.[9,10] EDS is highly prevalent in untreated OSA, and it is estimated that 9% to 22% of patients with OSA continue to experience persistent daytime sleepiness despite the use of primary treatment modalities such as continuous positive airway pressure (CPAP).[11,12]

IMPORTANCE OF GOOD SLEEP

The AASM considers sleep of sufficient quantity and quality to be as essential to health as good nutrition and exercise.[13] Indeed, sleep is essential for survival. Animal models have demonstrated fatal outcomes following prolonged sleep deprivation, and human studies suggest that chronic sleep deprivation may be associated with increased mortality.[13] Chronic sleep deprivation

Table 1. Major disorders associated with EDS[2,3,6]

Medical and Psychiatric Disorders Associated With EDS	Sleep Disorders Associated With EDS
• Parkinson's disease • Multiple sclerosis • Metabolic encephalopathy (eg, chronic renal insufficiency, metabolic disorders, etc) • Endocrine abnormalities • Head trauma • Medications • Illicit drug use • Depression • Brain tumors, infections, or other CNS lesions	Sleep-Related Breathing Disorders • Obstructive sleep apnea • Central sleep apnea syndrome • Hypoventilation disorder • Sleep-related hypoxemia Central Disorders of Hypersomnolence • Narcolepsy (types 1 and 2) • Idiopathic hypersomnia • Kleine-Levin syndrome • Insufficient sleep syndrome Circadian Rhythm Sleep-Wake Disorders • Delayed sleep-wake phase disorder • Advanced sleep-wake phase disorder • Irregular sleep-wake rhythm disorder • Non–24 hour sleep-wake rhythm disorder • Jet lag or shift work

leads to cognitive and motor dysfunction that may increase the risk for motor vehicle and home- or work-related accidents.[13] One study found the motor and cognitive impairments associated with chronic sleep deprivation to be comparable to impairments induced by blood alcohol at or above the legal limit for driving.[14] Drowsy driving may be involved in a substantial number of motor vehicle accidents.[8]

Figure 1. The Epworth Sleepiness Scale[18]

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): ____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (eg, a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

Thank you for your cooperation.

ASSESSMENT OF EDS

The diagnosis of EDS can be challenging due to its many causes and to the way patients describe their symptoms. In describing how they feel, patients usually use the word "sleepy," but may also describe themselves as "fatigued" or "tired." Frequently they are sleepier than they realize.[15] Beyond a targeted and detailed medical history and physical examination, several objective and subjective tools are available to facilitate the identification and assessment of EDS, as described below.

Objective sleep tests administered by a healthcare professional include the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT). The MSLT measures the physiological ability to fall asleep during quiet times and is a standard objective assessment tool of sleepiness.[1,16] In general, the mean sleep latency cutoff that identifies abnormal sleepiness using the MSLT is 10 minutes—8 minutes is the cutoff required for diagnosis of narcolepsy—while mean latencies >10 minutes may fall within the normal range of sleepiness.[1,17]

The 40-minute protocol of the MWT is used to measure alertness and is helpful in assessing the ability to remain awake; however, the predictive value for assessing risk and safety has not been established for either the MWT or the MSLT. A mean sleep latency score using the 40-minute MWT of <8 minutes is considered abnormal; however, values >8 minutes but <40 minutes are of uncertain significance, and extrapolation of risk to real-world situations is not firmly established. Although there is no consensus on what magnitude of change is clinically significant, the direction of change may supplement clinical judgment in determining response to treatment.[16]

Subjective or patient-reported tests include Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). The ESS questionnaire was designed to assess the presence and severity of daytime sleepiness in a simple, standardized way.[3,18] The self-administered eight-question survey (Figure 1) asks subjects to rate (on a scale of 0-3) how likely they would be to fall asleep in a variety of situations, some known to be more sleep inducing than others.[18] The higher the score, the more indicative of increasing sleepiness; a score of >10 indicates abnormal daytime sleepiness, while a score of >15 is considered severe daytime sleepiness.[3]

Results obtained from the objective MSLT and the subjective ESS do not always correlate with each other, so guidelines recommend combining them with clinical judgment.[1]

The FOSQ is designed to assess the impact of sleepiness on the ability to conduct normal daily activities (ie, functional status). The original questionnaire contains 30 questions and has demonstrated validity and reliability, but may be cumbersome to use in clinical practice. A shorter, 10-question version has been developed and performs similarly to the original in assessing the consequences of functional impairment and response to treatment.[19]

ETIOLOGY OF EDS

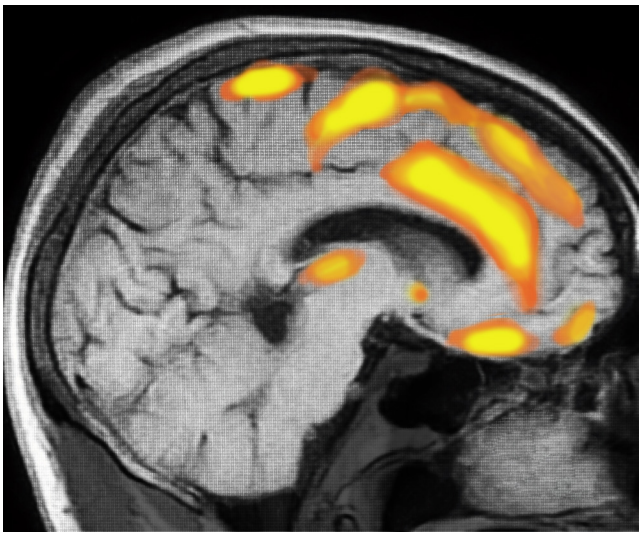
The neurobiology of sleep and wakefulness is increasingly becoming understood. Every day the body cycles between an awake state and a sleep state, which is referred to as the sleep-wake cycle. Each phase of this cycle is maintained by interdependent neurological pathways and neurochemicals. Specific neuronal groups in the brain fire in a characteristic pattern to promote arousal. However, during sleep the arousal system is inhibited by sleep-active neurons, including those of the ventrolateral preoptic nucleus (VLPO). The sleep-active neurons and the arousal pathways inhibit each other and thus may function like an on-off switch, allowing the body to maintain distinct states of wakefulness and sleep.[20] Normally, the aforementioned switch allows the body to maintain stability between sleep and wakefulness, while still allowing relatively rapid transitioning between the two states. Sleep disorders can result from an instability in this system by allowing periods of wakefulness to disrupt sleep and/or sleep to disrupt periods of wakefulness.[20-22]

MECHANISMS OF EDS IN OSA

OSA is characterized by repeated partial (hypopnea) or complete (apnea) obstruction of the pharyngeal airway, resulting in intermittent episodes of hypoxia and sleep fragmentation.[20,23] Episodes of apnea or hypopnea can lead to arousal, hypoxemia or hypercapnia, and abnormally high sympathetic nervous system activity.[20]

Animal models of sleep apnea have shown that repeated hypoxia/reoxygenation events lead to residual wake impairments that are associated with oxidative damage in several wake-active regions of the brain.[24] In mice, irreversible wake impairments were observed following exposure to long-term, intermittent hypoxia that were associated with the loss of dopaminergic neurons in the periaqueductal gray and noradrenergic neurons in the locus coeruleus.[24] Long-term sleep fragmentation, a different model of sleep apnea, was found to impair wakefulness and contribute to metabolic dysfunction and degeneration in 2 key wake promoting neuronal groups: noradrenergic neurons in the locus coeruleus and orexigenic neurons.[25]

Figure 2. Decreased gray matter concentrations in the brains of severe OSA patients[26]

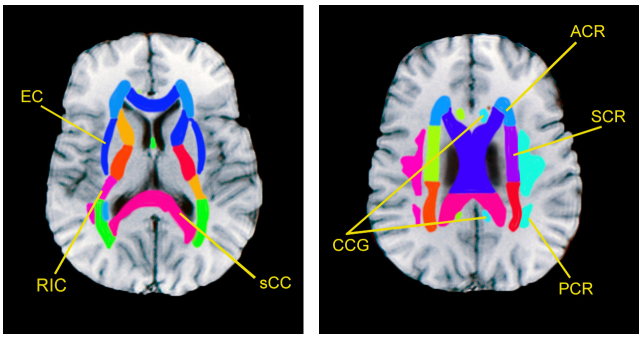


Statistical map showing reduced gray matter concentration in select brain regions of patients with severe OSA, including the frontal cortex, anterior cingulate cortex, and the thalamus. Image adapted with permission from *Sleep*.[26] Copyright © 2016, John Wiley and Sons.

Neuroimaging studies in humans generally suggest that OSA is associated with alterations in gray matter.[26-29] One pivotal study of patients with severe OSA found significantly reduced gray matter concentration in several key cortical and subcortical regions as compared to healthy controls (Figure 2). Other key studies have identified alterations in gray matter volume in several brain regions and suggest these changes may contribute to cognitive impairment associated with OSA.[27-29] Neurocognitive problems such as deficits in attention, visuoconstructive abilities, and memory can be associated with OSA.[23,26,27,30] Treatment with CPAP has been reported to at least partially reverse some structural and cognitive deficits associated with OSA.[30]

Recent imaging studies found that CPAP-compliant OSA patients with EDS had alterations in white matter structure based on diffusion tensor

Figure 3. White matter changes were found in the brains of OSA patients with persistent sleepiness. Key regions analyzed are shown below.[23]



ACR=anterior corona radiata; EC=external capsule; CCG=cingulum (cingulate gyrus); RIC=retrolenticular part of internal capsule; PCR=posterior corona radiata; sCC=splenium of corpus callosum; SCR=superior corona radiata.

Image adapted with permission from *Journal of Magnetic Resonance Imaging*.[23] Copyright © 2016, John Wiley and Sons.

imaging and non-Gaussian diffusion modeling.[23,31] In a study of OSA patients who were sleepy despite CPAP use, Xiong et al demonstrated that, compared to non-sleepy patients, sleepy patients had structural changes in the white matter consistent with compromised neuroconnectivity. Select white matter tracts analyzed in this study are shown in Figure 3.[23] In a recent study further supporting this finding, Zhang et al used non-Gaussian diffusion modeling to identify extensive alterations in the white matter tracts of patients who were sleepy despite CPAP use.[31]

Based on population studies, it is estimated that about 9% to 22% continue to experience EDS (as measured by ESS) despite CPAP use.[11,12] Studies based on clinical populations, such as those by Antic et al and Weaver et al, also suggest a high-level of persistent sleepiness with compliant CPAP use.[17,32] Antic et al studied the effects of 3 months of CPAP therapy on subjective and objective measures of daytime sleepiness, neurocognitive function, and quality of life in patients with moderate to severe OSA. Among patients with baseline abnormal ESS scores who used CPAP for more than 5 hours per night, 34% had abnormal ESS scores at the conclusion of the trial.[32] Weaver et al studied 149 patients with severe OSA and an apnea-hypopnea index (AHI) of ≥15 at baseline. Daytime sleepiness was measured subjectively using the ESS and objectively using the MSLT.[17] Despite use of a CPAP machine for ≥6 hours per night, a fifth of the participants (22.2%) reported subjective daytime sleepiness, and over half (52.2%) displayed objective evidence (MSLT) of residual daytime sleepiness. Even among patients who reported using CPAP for ≥7 hours per night, the percentage that achieved normal values was less than 100% for all outcomes.[17] These results demonstrated that even with adherence to CPAP therapy, a significant percentage of patients continued to experience daytime sleepiness.[17,32]

CONSEQUENCES OF EDS

Although patients with CPAP-treated OSA may experience improvements in quality of life, EDS associated with OSA still impacts the lives of patients.[17] Because some OSA patients continue to experience EDS despite adherence to CPAP treatment, effects of excessive sleepiness are an issue for many. It has been suggested that skipping even one night of CPAP treatment may reverse improvements gained in daytime sleepiness and performance.[33-35] Impaired concentration and EDS experienced by patients with OSA may impact performance of work and daily activities.[4,36] One study reported up to 90% of participants with EDS in OSA experienced a present or past unfavorable impact on work with most participants reporting impaired ability to complete detail-oriented tasks.[4] The National Safety Council estimates a loss to employers of approximately $136 billion annually in health-related lost productivity due to sleepy workers.[8]

Aside from the physical and psychosocial issues associated with EDS, the patient's impairment in the ability to drive a vehicle, presents a very real danger.[1,4] Studies have shown that people with OSA may be poor drivers with high collision rates. Based on a meta-analysis of studies investigating the relationship between collisions and OSA, it was estimated that over 800,000 drivers were involved in OSA-related motor vehicle collisions in 2000. These collisions resulted in 1,400 fatalities and the associated cost burden was estimated at $15.9 billion.[37]

TREATMENT OPTIONS AND GUIDELINE RECOMMENDATIONS FOR EDS ASSOCIATED WITH OSA

For patients with EDS associated with OSA, the American College of Physicians (ACP) and AASM both strongly recommend CPAP as initial therapy based on moderate-to-high-quality evidence demonstrating reduction in AHI scores, improvement in ESS scores, reduced arousal index scores, and increases in minimum oxygen saturation (Table 2).[38,39] The goal of CPAP treatment

is to alleviate airway obstruction during sleep.[38] Treatment of OSA with CPAP may improve cognitive and executive function,[40] and measures of cardiovascular disease including hypertension, and fatal and non-fatal cardiovascular events.[41] Several observational studies showed statistically significant reductions in overall and cardiovascular mortality rates with CPAP use (or adherence) compared to no CPAP use (or nonadherence), but randomized controlled trials have not been able to confirm this benefit.[38]

In evaluating methods of airway management in OSA, the AASM reviewed over 35 randomized, controlled trials (RCTs) and meta-analyses assessing the efficacy of positive airway pressure (PAP) methods to reduce daytime sleepiness. They found an overall high quality of evidence to recommend using PAP versus no treatment as initial therapy for adults with OSA and no significant comorbidities (congestive heart failure, significant lung disease, and neuromuscular disease).[39]

The AASM particularly recommends either CPAP or auto-adjusting PAP (APAP); however, the AASM does also recommend CPAP or APAP for the routine treatment of OSA over bi-level CPAP (BPAP; all devices), which are designed to alleviate the difficulty and discomfort of exhaling against the fixed pressure of CPAP by delivering lower pressure during exhalation than during inhalation.[39]

Dental or mandibular advancement devices (MADs) are designed to be worn while the patient is sleeping and are recommended as potential alternatives to CPAP in OSA patients with adverse effects associated with, or an aversion to CPAP. Although MAD use has been shown to improve AHI score, arousal index score, and minimum oxygen saturation compared to no treatment, moderate quality evidence from 10 studies has demonstrated that CPAP is superior to MADs in these measures.[38]

Alternative treatment approaches to OSA include surgery to remove obstructive tissue, weight loss in

Table 2. ACP and AASM clinical guideline recommendations for the management of OSA with PAP in adults[38,39]

	ACP 2013[38]	AASM 2019[39]
Recommendation 1	ACP recommends that all overweight and obese patients diagnosed with OSA should be encouraged to lose weight (Grade: strong recommendation; low-quality evidence)	The AASM recommends that clinicians use PAP, compared to no therapy, to treat OSA in adults with excessive sleepiness (Grade: strong recommendation; high-quality evidence)
Recommendation 2	ACP recommends continuous positive airway pressure treatment as initial therapy for patients diagnosed with OSA (Grade: strong recommendation; moderate-quality evidence)	The AASM recommends that clinicians use PAP, compared to no therapy, to treat adults with OSA and impaired sleep-related quality of life (Grade: conditional recommendation based on moderate-strength evidence)
Recommendation 3	ACP recommends mandibular advancement devices as an alternative therapy to continuous positive airway pressure treatment for patients diagnosed with OSA who prefer mandibular advancement devices or for those with adverse effects associated with continuous positive airway pressure treatment (Grade: weak recommendation; low-quality evidence)	The AASM recommends initiating therapy with either APAP or CPAP over BPAP for the routine treatment of OSA in adults (Grade: strong recommendation for ongoing treatment using CPAP/APAP; moderate-quality evidence) (Grade: conditional recommendation for the use of CPAP/PAP vs BPAP; very low quality of evidence)

AASM=American Academy of Sleep Medicine; ACP=American College of Physicians; APAP=auto-adjusting PAP; BPAP=bi-level CPAP; CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea; PAP=positive airway pressure.

appropriate patients (guideline recommendation), and positional therapy. Currently, the ACP Guidelines provide recommendations for the treatment of airway obstruction associated with OSA and do not include a review of clinical trials investigating treatments for EDS in OSA.[38]

Several FDA-approved pharmacologic options exist to address EDS associated with OSA (Table 3).[42-45] and there are other treatments that have been used off-label but are not approved for this indication by the FDA.[46] Wake-promoting agents should be used alongside, but are not intended to replace primary airway therapy.[43-45]

Table 3. FDA-approved pharmacologic options to treat EDS in OSA[42-45]

FDA-approved wake-promoting medications to treat EDS in OSA
Modafinil
Armodafinil
Solriamfetol

SUMMARY

EDS is characterized by sleepiness that is likely to occur during periods of inactivity, boredom, or monotony, and may be remedied, only temporarily, by sleep.[1,2] EDS is a common symptom of OSA[2] and can have lasting and significant physical and psychosocial consequences on patients, such as impairment in the ability to work, and impact on family and relationships.[1,4] In addition, chronic EDS impairs cognitive processing[23,26,27,30] and can potentially make driving a vehicle dangerous.[1,4]

Many studies have indicated that OSA is associated with changes in brain structure. Of note, recent studies have indicated that CPAP-treated patients with persistent sleepiness exhibit alterations in their white matter, suggesting potentially permanent damage that may compromise neuroconnectivity and hinder functional recovery.[23,31]

The goal of the management of OSA patients is to alleviate airway obstruction during sleep, while the goal of treatment of EDS is to reduce daytime sleepiness, potentially allowing patients to return to home and social activities, work, and school.[38,47]

For patients with EDS associated with OSA, the ACP and AASM strongly recommend CPAP as the primary treatment for OSA.[38,39,42] However, an estimated 9% to 22% of CPAP-treated patients have reported that EDS can persist despite use of primary OSA therapy.[11,12] For patients with persistent EDS in OSA, despite CPAP use, pharmacologic therapy may be added for appropriate patients.[43-45] The AASM clinical guidelines recommend options for the pharmacologic treatment of patients with OSA, including an FDA-approved agent that addresses EDS associated with OSA.[42]

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