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### CME Objective

After studying this article, you should be able to:

- Select and monitor pharmacologic and nonpharmacologic treatments for narcolepsy, obstructive sleep apnea, and other sleep disorders

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### Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Zynx Health and Bloom Burton, has received grant/research support from Pfizer, and has been a stock shareholder of Healthcare Technology Systems. No member of the CME Institute staff reported any relevant personal financial relationships.

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## Managing Excessive Daytime Sleepiness

Thomas Roth, PhD, and Russell P. Rosenberg, PhD

**E**xcessive daytime sleepiness (EDS) is common in clinical practice, with the National Sleep Foundation's *Sleep in America* poll<sup>1</sup> finding that about 18% of respondents qualified as excessively sleepy. Negative effects of EDS include decreased quality of life, cognitive impairment, poor work performance, poor medical health, and motor vehicle accidents.<sup>2,3</sup> To avoid these problems, clinicians must assess patients for EDS and associated conditions and provide appropriate treatment.

### ASSESSMENT OF EDS

Due to the negative effects of EDS, clinicians should routinely assess patients' sleepiness. In the clinical interview, questions must be worded carefully. Simply asking patients if they are tired during the day is not informative because most people experience some daytime tiredness. Better questions to identify clinically relevant sleepiness are "Do you ever unintentionally fall asleep," "Do you feel fully alert throughout the day," and "Do you persistently have to fight off sleep at work or school?" To evaluate the severity of patients' EDS, clinicians may also use patient-report scales and objective tests.

### Patient-Report Scales

The Epworth Sleepiness Scale (ESS)<sup>4</sup> is the mostly widely used self-report measure of sleepiness.<sup>3</sup> When completing the ESS, patients are asked to rate the likelihood that they would fall asleep in 8 situations such as reading or waiting in traffic.<sup>4</sup> A score of 10 or above indicates pathological daytime sleepiness.

Other patient-rated scales include the Karolinska Sleepiness Scale, the Stanford Sleepiness Scale, and the Sleep-Wake Activity Inventory.<sup>5</sup> While these tests are not as well validated as the ESS for assessing sleepiness, they can be used to track symptoms over time.<sup>5</sup> Validated patient questionnaires are generally efficient for clinical practice but are subject to errors of patient bias as well as cognitive or memory impairments. These problems can be offset by questioning patients' family members or friends to obtain another perspective.

### Objective Measures

A number of objective measures can be useful for assessing causes of EDS. Polysomnography tests patients for sleep-disordered breathing or abnormal movements during sleep. It typically requires an overnight stay to monitor neurophysiologic and cardiorespiratory variables.<sup>5</sup> Actigraphy is a cost-effective measure of movement and sleep/wake patterns over days or weeks, rather than just overnight, and is useful for diagnosing insomnia, circadian rhythm disorders, or EDS due to insufficient sleep.<sup>6</sup> If obstructive sleep apnea (OSA) is thought to be contributing to EDS, home sleep apnea testing devices can be used to measure breathing during sleep, but they do not provide an objective measure of sleepiness.<sup>7</sup>

The gold standard objective measure of excessive sleepiness is the Multiple Sleep Latency Test (MSLT).<sup>5</sup> The MSLT is conducted in a sleep

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The teleconference was chaired by **Thomas Roth, PhD**, Henry Ford Hospital Sleep Center, Detroit, Michigan. The faculty was **Russell P. Rosenberg, PhD**, NeuroTrials Research and Atlanta School of Sleep Medicine and Technology, Georgia.

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laboratory and determines the amount of time until sleep initiation and whether rapid eye movement sleep is achieved.<sup>8</sup> Falling asleep in less than 10 minutes is generally considered abnormal, and a sleep latency under 5 minutes indicates severe sleepiness.<sup>8</sup> Another objective test is the Maintenance of Wakefulness Test (MWT), which is used to assess patients' ability to stay awake while seated in a quiet, dim room.<sup>8</sup> Unlike the MSLT, the MWT cannot be used to make a diagnosis. Neither test should be used in the absence of clinical history and polysomnography to diagnose a disorder involving EDS.<sup>5</sup>

## DISORDERS ASSOCIATED WITH EDS

EDS is associated with a variety of sleep disorders, medical and neurologic conditions, and psychiatric disorders (Table 1).<sup>3,5,9</sup> By considering these conditions and ruling out medication side effects and behaviors that cause sleep deprivation, clinicians can differentiate what is causing or contributing to EDS, which may be more than one condition.

### Sleep Disorders

If the patient's EDS is not caused by poor sleep hygiene, medication side effects, or insufficient sleep time, it may be a symptom of sleep-related breathing disorders, hypersomnias, sleep-related movement disorders, or circadian rhythm sleep disorders.<sup>3,10</sup>

### Medical and Neurologic Conditions

Medical and neurologic disorders are a common cause of EDS. In a community sample of 2,612 individuals without sleep-disordered breathing, narcolepsy, or shift work disorder,<sup>9</sup> 67% reported a medical disorder, and over 30% of those had EDS. Ulcers, migraines, and depression were independent

**Table 1. Contributors to Excessive Daytime Sleepiness<sup>a</sup>**

Medical conditions	Cancer Chronic renal failure Congestive heart failure Liver failure Obesity hypoventilation syndrome Ulcer
Neurologic conditions	Epilepsy Migraine Multiple sclerosis Parkinson's disease Stroke
Psychiatric conditions	Anxiety disorders Mood disorders Posttraumatic stress disorder Psychotic illness
Sleep disorders	Circadian rhythm sleep disorders (eg, shift work) Hypersomnias (eg, narcolepsy, parasomnias) Obstructive sleep apnea Periodic limb movement disorder Restless legs syndrome
Other factors	Insufficient sleep syndrome Poor sleep hygiene

<sup>a</sup>Based on Slater and Steier,<sup>3</sup> McWhirter et al,<sup>5</sup> and Stroe et al.<sup>9</sup>

predictors of EDS. Prevalence rates for EDS were 50% in those with ulcers; close to 40% in those with neurologic disorders, migraines, depression, and heart disease; and 24% and 19% for those with thyroid disorders and cancer, respectively.<sup>9</sup> Other conditions associated with EDS are rheumatoid arthritis, fibromyalgia,<sup>11</sup> head trauma, encephalitis, stroke,<sup>2</sup> multiple sclerosis, epilepsy, Parkinson's disease, and Alzheimer's disease.<sup>8</sup>

### Psychiatric Disorders

Psychiatric disorders are also often associated with EDS.<sup>8</sup> An epidemiologic study<sup>12</sup> found psychiatric disorders in 47% of individuals with hypersomnia but in only 16% of those without sleep complaints. Depression, bipolar disorder, posttraumatic stress disorder, and alcohol dependency are all associated with sleep/wake impairments, and their treatments may also produce iatrogenic effects on sleep.<sup>2,13</sup> Conversely, many sleep disorders can lead to psychiatric symptoms.<sup>13</sup> For example, OSA is associated with depression<sup>3</sup> and recurrent hypersomnia with hallucinations, binge eating, and irritability.<sup>14</sup> Because sleep disturbances affect outcomes in psychiatric disorders, measuring and treating EDS is a critical part of psychiatric treatment.<sup>13</sup>

## TREATMENT OF EDS AND RELATED CONDITIONS

The goals of treatment should be to reduce EDS and increase alertness, thereby improving psychosocial and occupational functioning and safety. Effective management of EDS typically involves both behavioral and pharmacologic interventions.

### Behavioral Strategies

Focusing on patients' sleep hygiene is an important first step to improving EDS. Patients should adhere to a consistent sleep/wake schedule, exercise regularly (but not within 3 hours of bedtime), maintain a comfortable bedroom environment,

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**Table 2. Recommended Sleep Duration in Hours by Age Group<sup>a</sup>**

Age, y	Recommended	Not Recommended
Teenager, 14–17	8–10	<7 or >11
Young adults, 18–25	7–9	<6 or >11
Adults, 26–64	7–9	<6 or >10
Older adults, ≥65	7–8	<5 or >9

<sup>a</sup>Based on Hirshkowitz et al.<sup>16</sup>

and avoid heavy meals, alcohol, caffeine, and smoking before bedtime.<sup>15</sup> Individuals must also ensure they are allowing themselves enough sleep time within the recommended range for their age group (Table 2).<sup>16</sup>

**Disorder-Specific Pharmacologic Treatments**

Practice guidelines and US Food and Drug Administration (FDA)-approved treatments are available for many, but not all, of the disorders associated with EDS. Best practices for managing EDS vary depending on the underlying disorder.

**Narcolepsy.** In most cases, individuals with narcolepsy, particularly those who experience cataplexy, require lifelong treatment because the orexin deficiency underlying this disorder is permanent.<sup>17</sup> In addition to adhering to good sleep hygiene, patients with narcolepsy require pharmacotherapy. Several agents are available for the treatment of EDS and cataplexy associated with narcolepsy.

Sodium oxybate may be considered a first-line treatment option because it is the only agent with strong evidence of efficacy for both EDS and cataplexy and is FDA-approved for these indications.<sup>17,18</sup> It also may improve disturbed nocturnal sleep, sleep paralysis, and hypnagogic hallucinations.<sup>17,18</sup> However, this agent has a short half-life and brief duration of action, requiring the patient to take it at bedtime and to set an alarm for a second dose.<sup>17</sup> Sodium oxybate also can cause severe withdrawal symptoms and be fatal in overdose, but usually this occurs only when other agents are also being used.<sup>17</sup> Symptoms of anxiety or depression may occur,<sup>19</sup> and all patients should be questioned about current or past suicidal ideation or behavior.<sup>20</sup> Finally, sodium oxybate has been abused because of its rapid sedative properties, and therefore its use is restricted.<sup>17</sup> Both prescribers and patients must go through registration and training,<sup>20</sup> and all prescriptions are filled through a central pharmacy.<sup>17</sup> Despite these limitations, sodium oxybate is a safe and effective agent for narcolepsy when prescribed and taken correctly.<sup>17</sup>

The wakefulness-promoting agents modafinil and armodafinil are also approved for treating EDS associated with narcolepsy. When cataplexy is not present, modafinil or armodafinil can be considered a first-line option.<sup>19</sup> Both modafinil and armodafinil are well tolerated, but clinicians should educate female patients about potentially reduced effectiveness of some oral contraceptives.<sup>19</sup> Patients should also be warned to immediately report rashes or allergic reactions.<sup>21,22</sup> The stimulant methylphenidate and several amphetamines are FDA-approved for treating EDS, but because of their abuse potential, side effect profiles, and limited evidence, they should be considered only if sodium

- Patients may be experiencing negative effects from EDS that influence their safety, work performance, and overall health.
- Clinicians should collect a thorough history during the patient interview and use patient-report and objective tests to assess for EDS and associated conditions.
- Treatment for EDS varies depending on the underlying cause, but behavioral strategies and pharmacologic treatments are available to improve patients' symptoms.

Clinical Points

oxybate or modafinil/armodafinil have not resulted in desired outcomes.<sup>18,19</sup>

Treatments for cataplexy include not only sodium oxybate but also off-label antidepressants. The greatest evidence exists for the use of norepinephrine reuptake inhibitors, particularly venlafaxine and duloxetine, but selective serotonin reuptake inhibitors and tricyclic antidepressants are sometimes used.<sup>17–19</sup> These agents may improve cataplexy, but whether they also improve sleep paralysis and hypnagogic hallucinations is uncertain,<sup>17–19</sup> and they do not improve EDS. Individuals taking antidepressants may experience sexual dysfunction, gastrointestinal upset, and dry mouth.<sup>17,19</sup> Atomoxetine, a norepinephrine reuptake inhibitor that is used to treat attention-deficit/hyperactivity disorder, is also used for cataplexy and may alleviate EDS via stimulant effects.<sup>17,23</sup>

**Idiopathic hypersomnia.** No FDA-approved treatments are available for idiopathic hypersomnia, but the treatment of EDS associated with idiopathic hypersomnia is similar to that of narcolepsy. Practice guidelines<sup>18</sup> suggest the use of modafinil and methylphenidate or other stimulants. Most patients are able to benefit from monotherapy with one of these drugs.<sup>24</sup> A novel approach to idiopathic hypersomnia is to administer drugs that inhibit  $\gamma$ -aminobutyric acid (GABA) production.<sup>25</sup> Studies examining these compounds in the population are underway.

**Obstructive sleep apnea.** Combating EDS associated with OSA should begin with attempts to improve the quality of nighttime sleep by addressing the upper airway obstruction. In some individuals, weight loss and position training can lead to improvement.<sup>26</sup> Other individuals will require treatment with a positive airway pressure device or an oral appliance.<sup>27</sup> Some patients continue to experience EDS despite receiving treatment for OSA and may benefit from an adjunctive agent during the day<sup>28</sup>; modafinil and armodafinil are approved for treating EDS associated with OSA.

**Shift work disorder.** Shift work disorder occurs in individuals who must be awake and alert when their body's circadian clock says they should be asleep, and vice versa.<sup>29</sup> Night shift workers are vulnerable to this disorder as well as individuals who rotate shifts frequently. Behavioral interventions include improving sleep hygiene, using timed light exposure, and scheduling naps.<sup>30</sup> Sedative hypnotics or melatonin may be used to combat insomnia and ensure individuals get a sufficient amount of sleep.<sup>30</sup> If sleepiness persists during working hours, stimulants may be used. Modafinil and armodafinil are both approved for the treatment

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of EDS associated with shift work disorder. Amphetamines can increase alertness but are not recommended because of their abuse potential.<sup>30</sup>

**Kleine-Levin syndrome and Parkinson's disease.** No FDA-approved treatments are available for EDS associated with Kleine-Levin syndrome or Parkinson's disease, but modafinil may be effective.<sup>8</sup>

**CONCLUSION**

Unrecognized and untreated EDS can endanger patients' safety, reduce their function at work or school, and negatively impact their health. Clinicians can assess EDS using appropriate questions during the clinical interview, patient-report questionnaires such as the ESS, and objective tests such as polysomnography and the MSLT. Patients should be encouraged to develop good sleep habits and get sleep within the recommended range for their age. By recognizing conditions that may be causing EDS, clinicians can develop a treatment plan to target EDS and associated conditions. Pharmacologic treatments are available to improve EDS in sleep disorders such as narcolepsy and OSA, while other conditions are not as well researched. Using a combination of behavioral and pharmacologic strategies will enable clinicians to improve the safety and quality of life for patients with EDS.

**Drug names:** armodafinil (Nuvigil), atomoxetine (Strattera), duloxetine (Cymbalta and others), methylphenidate (Daytrana, Concerta, and others), modafinil (Provigil and others), sodium oxybate (Xyrem), venlafaxine (Effexor and others)

**Disclosure of off-label usage:** Dr Roth has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

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**POSTTEST**

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1. Ms A, your 58-year-old patient with obstructive sleep apnea, presents with excessive daytime sleepiness (EDS), even though she is consistently sleeping with her positive airway pressure device. What additional treatment would be the best option to improve her EDS?
  - a. Armodafinil/modafinil
  - b. Atomoxetine
  - c. Methylphenidate
  - d. Sodium oxybate
2. Mr B, a 26-year-old new patient, presents with EDS based on his interview and Epworth Sleepiness Scale score of 14. To manage his 2 part-time jobs and college courses, he relies on energy drinks and caffeine. What would be the best treatment strategy for him?
  - a. Lessen his caffeine intake and start a wake-promoting agent (eg, modafinil)
  - b. Keep using caffeine as necessary but try to increase total sleep time
  - c. Lessen his caffeine intake and increase total sleep time
  - d. Start stimulant therapy

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