Sleep-Disordered Breathing and Excessive Daytime Sleepiness

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KEYWORDS

• Sleep disorders • Sleep apnea • Excessive daytime sleepiness • Persistent sleepiness
• Hypersomnolence • Hypersomnia • Therapy • Treatment resistance

KEY POINTS

- Excessive daytime sleepiness is common in obstructive sleep apnea, although a significant number of patients lack this complaint.
- Excessive daytime sleepiness may coexist with other forms of sleep-related breathing disorders, but the evidence regarding this is less robust than for obstructive sleep apnea.
- Multiple methods are available to evaluate sleepiness, all of which have limitations including inconsistent correlation to presence and severity of obstructive sleep apnea.
- Data on amelioration of sleepiness with treatment of obstructive sleep apnea are most robust for positive airway pressure therapy, but improvement is seen with other treatment modalities.
- Before initiating pharmacotherapy for persistent sleepiness despite adequate control of obstructive sleep apnea, alternative causes of sleepiness should be evaluated and treated.

INTRODUCTION

The term sleep-disordered breathing encompasses the full spectrum of sleep-related respiratory disturbances. Sleep-related breathing disorders (SRBD) represent the subset that meets International Classification of Sleep Disorders Third Edition (ICSD-3) criteria as a disorder; abnormalities such as snoring or catathrenia are examples of entities not included under the term SRBD.[1] The ICSD-3 describes 4 different, but interrelated types of SRBD: (1) obstructive sleep apnea (OSA) syndrome, central sleep apnea (CSA) syndromes, sleep-related hypoventilation (SRH) disorders, and sleep-related hypoxemia disorder.[1] SRBD in the various forms may manifest as abnormal airflow, oxygen desaturation, or hypercarbia that can be associated with excessive daytime sleepiness (EDS). For OSA, EDS is a frequently reported symptom that is included as a possible clinical feature in the ICSD-3 diagnostic criteria, but a significant number of OSA patients do not report this symptom. Here we discuss the relationship between EDS and SRBD focusing primarily on OSA. We review patient factors related to EDS, treatment options, evaluation and treatment of persistent sleepiness despite treated OSA, and future developments.

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EXCESSIVE DAYTIME SLEEPINESS

A standard definition for EDS is lacking. It is often described as the inability to stay awake and alert during the day when the circadian sleep drive promotes alertness.[2] EDS can manifest as falling asleep unintentionally during routine daily activities or the subjective perception of sleepiness. Patients who do not report subjective sleepiness may nevertheless have objective sleepiness and vice versa. To further complicate matters, patients use a diverse vocabulary to describe the feeling of sleepiness including fatigue, tiredness, unrested, and lack of energy. Patients with EDS have lower quality of life, decreased workplace productivity, and increased risk of work-related injury.[3,4] In the United States, a general population survey noted a prevalence of 18% based on Epworth Sleepiness Scale (ESS) score of $\geq$10.[5] Population-based surveys from the National Sleep Foundation found that about 30% of respondents suffer from enough EDS to interfere with their quality of life.[6] Methods have been developed over the last 4 decades to subjectively and objectively measure EDS. The ESS is the most commonly used subjective instrument to assess EDS in clinical practice and research applications.[7] The Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) are well-established objective measures for EDS but are used infrequently in clinical practice because of their resource intensity and limited utility in the evaluation of patients with SRBD.[8]

EXCESSIVE DAYTIME SLEEPINESS IN SLEEP-RELATED BREATHING DISORDERS

OSA is the most common type of SRBD and also the disorder for which the most is known about with regard to EDS.

Obstructive Sleep Apnea Disorders

OSA is characterized by upper airway narrowing or closure during sleep with continued respiratory effort.[1] It is commonly thought that repetitive obstructions with and without intermittent nocturnal hypoxemia lead to sleep fragmentation, cortical arousals, awakenings, and inability to achieve and sustain more restful sleep stages resulting in EDS. The Wisconsin Sleep Cohort reported the prevalence of OSA syndrome (Apnea-hypopnea index [AHI] $\geq$5 with sleepiness) to be 4% in men and 2% in women.[9] Several other population studies on OSA associated with EDS found prevalences of 3% to 7% in men and 2% to 5% in women.[10] A more recent large population-based study found a prevalence of OSA syndrome (AHI $\geq$5 and ESS score $\geq$11) of 13% in men and 6% in women.[11] The higher prevalence is attributed to the increased prevalence of obesity and changes in the diagnostic and scoring criteria for OSA. OSA prevalence when defined by AHI alone is several-fold higher, indicating that a large percentage of OSA subjects do not complain of EDS.[9,11,12] The relationship between OSA and EDS is seem to be influenced by a host of factors and subject to considerable interindividual variability in susceptibility to sleepiness.

Central Sleep Apnea Syndromes

CSA syndromes are characterized by recurrent cessation or attenuation of respiratory effort during sleep.[1] CSA can be the result of distinct disease processes, most commonly heart failure (HF), atrial fibrillation, stroke, chronic kidney disease, and medications.[1] Recent analyses show a CSA prevalence of 0.9% to 3.5%.[13,14] Other systematic reviews report the prevalence of CSA to be 24% in the setting of opioid use—averaging 200 mg of morphine equivalent daily dose and 8% for treatment emergent CSA (TECSA).[15,16] There are little data on the relationship between CSA and EDS, which suggests that CSA may not be independently associated with EDS. A community-based study reported that those with CSA had a level of sleepiness comparable to those without SRBD and lower than those with OSA despite having higher AHI.[14] Furthermore, a study in stable HF patients found that the prevalence of EDS in those with CSA was not statistically different (16% vs 11%) than in those without CSA; EDS was associated with HF severity rather than sleep parameters.[17] Finally, a study in patients with atrial fibrillation found those with CSA had a lower prevalence of EDS than those with OSA.[18]

Sleep-Related Hypoventilation Disorders

The hallmark of SRH is abnormally elevated arterial pressure of carbon dioxide during sleep, although hypoventilation may also be present during waking hours.[1] Most of data regarding EDS and SRH come from patients with obesity hypoventilation syndrome (OHS). Because 90% of those with OHS also have OSA, it is unclear whether hypoventilation is playing an independent role.[19] OHS subjects were reported to have more EDS and higher ESS score compared with isolated OSA. However, this finding may be attributed to higher body mass index (BMI) and worse sleep parameters,[20] as one study found resolution of symptom differences after adjusting for obesity.[21] Yet another study found significantly higher ESS score in OHS patients compared with OSA