

subtle signs
OBSTRUCTIVE
SLEEP APNEA



Obstructive Sleep Apnea

Part 1

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Sleep phenomenon has fascinated researchers for many centuries, perhaps since the dawn of civilization. One need only to look at the classics to find philosophers' musings about sleep and dreams to see how much the human condition is tied to sleep.

As time progressed, our fascination with sleep deepened and we learned how the earth's rotation every 24 hours influenced the way many animals sleep and live. Hence, the study of circadian rhythms: human beings are supposed to feel sleepy when it is dark and wakeful when it is bright outside. Feeling sleepy when one is supposed to be wakeful is considered an abnormal condition called excessive daytime sleepiness or hypersomnolence.

Sleep has been part of psychiatry ever since sleep medicine erupted out of the research field and into clinical medicine. William

Dement, professor emeritus of the Stanford psychiatry program, is considered the father of sleep medicine; he established the world's first sleep medicine program in about 1960. Sleep disorders made their first appearance in DSM III-R as a separate disorder section in 1987, before the first International Classification of Sleep Disorders (ICSD)—the bible of sleep disorders—was published.

Currently, DSM 5 lists 13 different sleep disorders and additional "other" or "unspecified" disorders. Obstructive sleep apnea and hypersomnolence disorder are among the most difficult to diagnose and treat, since they have subtle clinical signs and symptoms that may overlap with other psychiatric diagnoses. The psychiatric field is concerned not only with symptoms of mental disorders but also somatic and unspecified symptoms that can occur throughout life in general (**Table 1**). Sleep hygiene is a top priority, especially in people with a mental illness.

Acronyms: CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness test; OSA, obstructive sleep apnea; PAP, positive airway pressure; PVT, Psychomotor Vigilance Test; SSS, Stanford Sleepiness Scale.

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Obstructive sleep apnea

Obstructive sleep apnea (OSA) often presents with obvious symptoms such as loud habitual snoring as well as subtle symptoms such as irritability, lack of motivation or energy, sleep disturbance, nightmares, decreased memory, attention deficit, and depression. A psychiatrist will often see patients who present with these symptoms. When these subtle symptoms accompany definitive breathing-related symptoms such as loud snoring, apnea or, choking/

gasping arousals, direct referral to a sleep lab for testing is indicated. When the breathing-related symptoms are not present or difficulty to elicit, a referral to a sleep specialist for possible sleep disorders, including sleep apneas and other major sleep disorders, might be indicated. The psychiatrist on his or her own, or in partnership with a sleep facility, will need to fully assess patients. (Important terminology is noted in **Table 2**.)

Assessing patients with OSA who complain of excessive daytime sleepiness

When a patient with known OSA presents with excessive daytime sleepiness (EDS) there are many things to investigate or rule out before establishing a diagnosis of “residual EDS despite adequate treatment of OSA using CPAP (continuous positive airway pressure).”

The first is to ensure that the positive airway pressure (PAP) setting is optimal. When a patient with OSA is using a PAP device but at the wrong setting, the results are similar to untreated OSA. EDS in suboptimally treated OSA is not very surprising. The intervention in this case is “PAP setting optimization.”

The second is to look at adherence. Despite the PAP device being in the optimal setting, if a patient is not using the device, EDS should be considered to be caused by untreated or suboptimally treated OSA. The conventional definition of PAP adherence is using it for more than 4 hours a night, more than 5 days a week, or 21 days per consecutive 30 days. If the patient is not using the PAP device at least for this amount of time, explain to him or her the need to increase the duration of PAP use.

The third is to check whether the patient is sleeping a sufficient number of hours. For example, despite being treated at the optimal PAP setting, if the patient is sleeping only 6 hours a night it will lead

TABLE 1 Medical conditions that can explain excessive daytime sleepiness

| SLEEP DISORDERS |
|---|
| Insufficient sleep syndrome, including insomnia |
| Obstructive sleep apnea |
| Obesity hypoventilation syndrome |
| Narcolepsy |
| Idiopathic hypersomnia |
| Shift-work disorder |
| Restless legs syndrome |
| Periodic limb movement disorder |
| OTHER MEDICAL CONDITIONS |
| Seasonal affective disorder |
| Chronic pain and fibromyalgia |
| Chronic fatigue syndrome |
| Hypothyroidism and many hormonal disorders |
| Sedating medications |

to chronic sleep deprivation. The EDS is explained by insufficient sleep syndrome, rather than residual EDS.

How many hours of sleep is enough?

Evidence suggests that to maintain treatment effects, nasal CPAP therapy for OSA needs to be used every night. What remains unknown is the nightly duration of use required to normalize functioning. A study published in 2007 estimated the likelihood of return to normal levels of sleepiness and daily functioning relative to nightly duration of CPAP.¹ There were significant differences in mean nightly CPAP duration between treatment responders and nonresponders across outcomes.

A linear dose-response relationship ($P < .01$) between increased use of CAP and achieving normal levels of sleep was shown for objective and subjective daytime sleepiness. Sleep hours required for better outcome varied depending on what measures were used. Thresholds above which further improvements were less likely relative to nightly duration were as follows: 4 hours with the Epworth Sleepiness Scale (ESS); 6 hours with the Multiple Sleep Latency Test (MSLT); and 7.5 hours with the Functional Outcomes associated with Sleepiness Questionnaire.

PAP devices are capable of showing adherence based on usage hours per night. In addition, they can help gauge the effectiveness of treatment by showing whether residual obstructive breathing events occur and how frequently they occur, via the apnea-hypopnea index (AHI).

Residual EDS in OSA: how to measure sleepiness, subjective vs objective

Once it is confirmed that OSA is adequately controlled using the optimally set PAP device with sufficient hours of sleep the funda-

TABLE 2 Commonly used acronyms in sleep medicine and sleep study

| | |
|-------------------------------------|---|
| Apnea-hypopnea index (AHI) | the score used to indicate the severity of sleep apnea as represented by the number of apnea and hypopnea events per hour of sleep |
| Epworth Sleepiness Scale (ESS) | a self-administered questionnaire to assess daytime sleepiness |
| Excessive daytime sleepiness (EDS) | a nonspecific symptom common in many sleep disorders; it is characterized by persistent sleepiness and/or a general lack of energy, even during the day after apparently adequate or even prolonged night sleep |
| Multiple Sleep Latency Test (MSLT) | the standard tool used to diagnose narcolepsy and idiopathic hypersomnia; assess excessive daytime sleepiness by measuring how quickly you fall asleep in a quiet environment during the day |
| Obstructive sleep apnea (OSA) | considered the most common type of sleep apnea; caused by complete or partial obstructions of the upper airway |
| Polysomnogram/polysomnography (PSG) | a multi-parametric test that measures brain waves, blood oxygen levels, heart rate and breathing; used to diagnose sleep disorders |
| Positive airway pressure (PAP) | therapy that uses a stream of compressed air to support the airway during sleep |

mental question is: "Is the patient truly sleepy?" Answering this question can lead to the correct treatment. For example, drug treatment using CNS stimulants or other drugs can promote wakefulness. However, a pharmacological adjunct to PAP treatment can be considered only after residual sleepiness is confirmed.

There are many different measures and tools to assess and define sleepiness. ESS is the most commonly used scale and it aims to assess the average level of sleepiness of the past 2 weeks in "what if" situations. The Standard Sleepiness scale (SSS), is a self-report that gauges the level of sleepiness on a scale of one to seven, ranging from feeling wide awake to sleep onset soon to longer fighting sleep. SSS aims to assess the level of sleepiness "at this moment" and as such, it is not a very clinically useful measure because level of sleepiness varies a great deal depending on the time of the day, duration of staying awake, use of substances, and so on. As such it is not a useful marker of whether someone is pathologically sleepy.

The Maintenance of Wakefulness test (MWT) and the MSLT are primarily used in sleep research for polysomnography monitoring to define sleep latency as a surrogate measure of sleepiness. The MWT requires the participant to stay awake; with the MSLT the participant is encouraged to fall asleep rather than fighting sleep onset.

Much of the literature has dichotomized EDS into subjective EDS and objective EDS based on whether the quantification is based on subjective reports (or easily manipulated objective testing, eg, Psychomotor Vigilance Test [PVT]) versus intensive objective monitoring (where manipulation of results is hard). Sleepiness based on scales such as ESS and SSS is considered subjective sleepiness, whereas sleepiness based on MWT or MST is considered objective sleepiness.

One recently published study compared the subjective versus objective sleepiness measures in a unique way. This study used inflammatory marker IL-6 as evidence of true pathophysiological change associated with sleepiness. Objective and subjective daytime sleepiness in 58 patients with OSA and EDS were measured by MSLT, ESS, and SSS; IL-6 and cortisol levels were assessed as well. Objective EDS (lower MSLT) in OSA patients was associated with significantly elevated IL-6 across 24 hours and decreased cortisol levels during the daytime. In contrast, subjective EDS (higher ESS/SSS) was not associated with either elevated IL-6 levels or decreased cortisol levels.² The researchers concluded that OSA with objective EDS is the more severe phenotype of the disorder associated with low-grade inflammation.

The same group of researchers also studied PVT as a possible measure of sleepiness in OSA. Although abnormal PVT results (increased number of lapses or slower reaction time) was associated with ESS, there was no significant correlation between PVT and MSLT, nor PVT and IL-6 levels. These findings suggest that PVT is associated with subjectively assessed sleepiness rather than objective sleepiness.³

In another study involving 1338 patients with OSA and 484 controls, sleepiness measured objectively using MSLT was associated with hypertension, whereas subjective sleepiness based on ESS was not associated with hypertension.⁴ These results not only suggest a

link between hypertension and sleepiness but also serve to show that subjective sleepiness may not be a reliable marker with true clinical implications.

These studies, which assessed the utility and validity of objective versus subjective sleepiness measures suggest that objective sleepiness measured by MWT or MSLT is more accurate and useful in the clinical management of residual EDS in OSA.

Epidemiology and etiology

Hypotheses have been made to explain the etiology of residual sleepiness. It has been suggested that neuronal injury and brain alterations from repeated hypoxemia before OSA treatment may cause sleepiness even after treatment. Other theories suggest that chronic sleep fragmentation causes degeneration of neurons involved in wake promotion. Nevertheless, there have been no well-designed pathophysiological studies to date. There are, however, some clues based on epidemiological studies, which may be used to determine clear etiology or risk factors for EDS.

Sleepiness in untreated OSA

A large Australian community cohort study comprised 788 undiagnosed random community subjects. Findings showed that 413 had a diagnosis OSA.⁵ Among those with OSA, 14% were positive for EDS defined by ESS greater than 10. The percentage of men with EDS was independent of OSA severity (no OSA: 12%; mild to moderate OSA: 14%; severe OSA: 14%). It is interesting to note that depression was associated with severe OSA. Moreover, there was a very strong correlation of depression and the combination of OSA and EDS.

In a study of 50 subjects with OSA, regression analysis showed that the AHI and the desaturation index were important predictors of daytime sleepiness in patients with OSA, which explains the 40% ESS score. Between the two indices, the desaturation index had the higher correlation with ESS.⁶

Prevalence of residual EDS in treated OSA

Prevalence of residual EDS in OSA despite adequate PAP treatment varies depending on what criteria are used to define OSA, PAP adherence, and excessive sleepiness. A French study from 2009 showed prevalence of 12%.⁷ This was based on adherence to PAP treatment of 3 hours or longer daily. When other causes of sleepiness were ruled out in this 12% of patients (60 out of 502), only 6% were thought to have residual EDS while being PAP-adherent.

Findings from a study undertaken to elicit factors that affect residual hypersomnolence showed that severe OSA (AHI greater than 30) had less prevalent residual hypersomnolence (11%) compared with moderate severity OSA with residual hypersomnolence (18%).⁸ The researchers concluded that hypoxic brain damage might not be the cause of residual EDS based on the fact that severe OSA was a protecting factor for residual EDS.

Predictors of residual excessive sleepiness in adequately CPAP-treated OSA may be due to a history of depression, diabetes, and heart disease, with a higher ESS score and lower desaturation index on initial assessment.⁹

Treatment

Pharmacology that can be used in residual EDS was developed based on the brain sleep-wake mechanism and its neurotransmitter. Monoamine neurotransmitters and receptors with wake-promoting activity are often the target of drug therapy. These monoamines include dopamine, norepinephrine, and histamine.

None-amphetamine CNS stimulants have been used for residual EDS in OSA. Thirty patients with OSA treated with PAP therapy were tested using either 400 mg modafinil or placebo for 2 weeks in a double-blind randomized crossover study.¹⁰ Modafinil had no effect on sleepiness as measured by ESS or MSLT. Some improvements in alertness were found with the MWT (modafinil 18.3 +/- 3.9 min; placebo, 16.6 +/- 5.0 min; $P < .02$).

A placebo-controlled trial of armodafinil involved 395 patients with residual EDS while being adherent to PAP therapy for OSA.¹¹ Subjects in the armodafinil group showed improvement in EDS measured by MWT.

Avellar and colleagues¹² performed a meta-analysis of 8 placebo-controlled clinical trials of either modafinil or armodafinil. Pharmacotherapy with modafinil and armodafinil led to improvement of excessive daytime sleepiness, attention/alertness, and clinical condition as measured by the CGI-C. They found that pharmacotherapy did not cause any severe adverse effects but was associated with significant dropout rates compared with placebo.

A clinical trial of 50 patients with residual EDS with treated OSA categorized participants based on the presence of objective sleepiness measured by MWT.¹³ Only those with objective sleepiness showed improvement with modafinil treatment. This indicates that improvement in sleepiness symptoms seems to be difficult to

achieve with modafinil treatment among subjects with less objective sleepiness.

There are two other types of drugs yet to be available for the use in residual EDS in OSA. One is a histamine inverse agonist (MK-0249) and the other is a dopamine/norepinephrine reuptake inhibitor (JZP-100).

Result of the clinical trial using MK-0249 was published in 2013.¹⁴ This study involved 125 subjects with PAP adherent OSA. The subjects were assigned one of the three treatment groups (MK-0249, modafinil, and placebo). MWT was used to measure primary outcomes. Results showed no significant difference between MK-0249 (2.1 min) vs placebo (1.2 min). Modafinil showed significant change (prolongation of sleep latency) by 5.9 min compared with placebo. Using subjective outcome measures such as ESS and PVT, MK-0249 showed slight improvement. However, there was a much higher number of adverse events reported in MK-0249 (17.5%) than placebo (0.9%) or modafinil (1.8%).

Currently in clinical trials is soliamfetol (JZP-110). This is a dopamine/norepinephrine reuptake inhibitor that showed efficacy in significantly improving sleepiness measured by MWT (12.7 min vs 0.9 min with placebo) in patients with narcolepsy.¹⁵ The drug is being tested in ongoing clinical trials for residual EDS in OSA. Preliminary results show efficacy in improving sleepiness measured by MWT in patients with residual EDS.¹⁶

These drugs target well-known wake-promoting neurotransmitters such as dopamine, norepinephrine and histamine. Other sleep-wake regulating neurotransmitters such as serotonin, hypocretin, gamma-aminobutyric acid, and acetylcholine might become a target of future drug development for this condition. ■

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Obstructive Sleep Apnea Hypersomnolence

Part 2: *A Clinical Case Discussion*

Hypersomnolence in a setting of treated obstructive sleep apnea (OSA) is a common problem, with patients presenting with sleep complaints in day-to-day psychiatric practice. Consider the case of EB, a 50-year-old man referred for evaluation and treatment of excessive daytime sleepiness.

EB was first seen by a psychiatrist for anxiety and depression. However, his symptoms were not typical anxiety or mood symptoms; he was irritable, nervous, fatigued, sleepy, and he had decreased productivity, and angry outbursts. His wife complained that he snored and he was sent to a sleep lab. Based on the polysomnogram that showed an apnea-hypopnea index of 15 and oxygen saturation of 80% RB was given a diagnosis of OSA. He has been adherent to positive airway pressure (PAP) therapy since the diagnosis; with no need for pressure setting adjustments.

Despite PAP therapy, many of his symptoms persisted. His psychiatrist started him on bupropion to help with depression and daytime sleepiness. With 300-mg bupropion daily, his mood improved slightly, and he became less irritable.

Referral visit to a sleep specialist: focusing on sleepiness

Despite PAP therapy and treatment of depression with bupropion, EB continued to experience severe excessive daytime sleepiness. After his psychiatrist and primary care physician discussed the options, he was sent to a sleep specialist for further evaluation and treatment.

EB noted that he often gets very sleepy while driving. Two years ago, he had had an accident when he fell asleep at the wheel. He admits that he was not using the PAP device before this incident because he had been camping. In addition to this isolated event, he reports generally having excessive daytime sleepiness including several episodes of sleep attack. He drinks coffee every day and this seems to be helping a bit. He has not tried any CNS stimulant medications.

To verify his PAP therapy adherence, he brings 2-months-adherence information from the PAP device. This shows 59/60 days of use, with 7 hours 18 minutes average use on days used, with an apnea-hypopnea index of 0.4 and average pressure of 12 CWP. He has been on an auto-PAP setting 6 to 16 CWP for the past several years without requiring pressure setting adjustment.

On average, EB sleeps seven and a half hours from 9 PM until 4:30 AM. He denies any snoring while on PAP therapy. He reports occasionally gasping and being very tired despite regular CPAP use. He reports falling asleep at work as soon as he is inactive or bored; no cataplexy events are reported.

EB had Multiple Sleep Latency Test (MSLT) 3 months ago. He did not keep a sleep diary or come off of his antidepressant before the test. The results showed a mean sleep latency of 3.9 minutes and 1 sleep-onset REM period. He has depression and hypertension. There is a strong history of OSA in male family members; the rest of his history and physical exams were unremarkable.

Assessment and Planning

What is the likely diagnosis? There can be many sleep disorders and non-sleep disordered medical conditions that can manifest with excessive daytime sleepiness. Initial differential diagnosis will often need to include the conditions listed in **Table 1** (see Part 1). Nevertheless, this case focuses on establishing the diagnosis of “residual excessive daytime sleepiness in treated OSA.”

First, we need to determine whether the PAP therapy setting is optimal. Based on the minimal number of residual events recorded in the PAP device, it can safely be assumed that the PAP setting is optimal. In addition, the patient is adherent to PAP therapy with 59 days use out of 60 days of the monitored time window. Sleep hours based on usage hour data also suggest that the patient is sleeping more than 7 hours with PAP on average. Now that we confirmed “treated OSA,” the next thing to determine is whether the patient is truly pathologically sleepy.

The patient presents with subjective excessive daytime sleepiness based on the Epworth Sleepiness Scale (ESS) score of 20 (**Table 3**). Among experts, an ESS score of 11 or higher is considered abnormal sleepiness. This patient’s ESS score is well above this threshold. Moreover, the patient’s results on the MSLT shows short sleep latency.

However the MSLT results may not be accurate. A polysomnogram was not done the night before testing. MSLT must follow an overnight polysomnogram, because sleepiness evaluation is valid only after good quality and quantity sleep the night before. Moreover, insufficient sleep amount for days to weeks prior to MSLT could not be ruled out because there is no documentation of the amount of sleep for 2 weeks prior to the sleep study. Anyone with insufficient sleep can manifest with the abnormally short sleep latency in MSLT. As such, despite the patient’s recent MSLT with short sleep latency, objective excessive daytime sleepiness could not be confirmed.

From the initial evaluation, thorough and valid evaluations were planned and performed in an effort to objectively assess excessive sleepiness.

Sleep study for objective assessment of excessive sleepiness

After scheduling a polysomnogram and MSLT sleep study, the patient was asked to stop using caffeine and alcohol for 2 weeks before the

sleep study. The patient was asked to log his sleep in a sleep diary for the same 2-week period. The patient was encouraged to use the PAP device when sleeping and was asked to bring the PAP data.

After ensuring sufficient duration of sleep with PAP—as recorded in the sleep diary—overnight polysomnogram was performed while the patient was using the PAP setting that he used at home (auto-PAP settings of 6–16 CWP). MSLT was done the next day. Using MSLT, the patient was encouraged to fall asleep during the recording and the time spent to go into sleep was closely monitored and measured as sleep latency. Mean sleep latency of 8 minutes or shorter is thought to indicate abnormal sleepiness.

MSLT was performed by monitoring EEG, EOG, and abdominal respiratory effort. During 5 nap attempts there was a mean sleep latency of 4.8 minutes during 5 nap tests. As expected, the results were unremarkable. The number of obstructive events was minimal, including supine REM sleep during which the patient would have experienced OSA if he were not on PAP therapy. EB went to sleep quickly with mean sleep latency less than 5 minutes, which confirmed objective EDS (**Table 4**).

TABLE 4 MSLT results for EB

| TEST | NAP 1 | NAP 2 | NAP 3 | NAP 4 | NAP 5 | MEAN |
|---------------------|-------|-------|-------|-------|-------|------|
| Sleep latency (min) | 5.5 | 7.5 | 2.5 | 3.5 | 5.0 | 4.8 |

Note: There were no sleep-onset REM periods; the results confirmed objective excessive daytime sleepiness.

Diagnosis and treatment

Based on these results, which confirmed objective EDS, the diagnosis of “residual excessive daytime sleepiness in treated OSA” was established. The patient started taking modafinil 200 mg once in the morning. With the addition of this CNS stimulant, the patient was able to better maintain wakefulness during the day with less caffeine use. His ESS score at the follow-up visit decreased to 12. The patient reported feeling “too much nerves” at times. However, he denied any major adverse effects from modafinil.

Conclusion

The clinical process in reaching the lengthy diagnostic name of “residual EDS despite treated OSA” is complicated. The main question to be answered after the evaluation of the patient is whether an adjunct drug therapy is indicated. Optimal CPAP treatment with a sufficient amount of nightly regular sleep is a pre-requisite. Residual sleepiness needs to be objectively measured using MWT or PSG/MSLT. When indicated, after the diagnosis is confirmed, non-amphetamine CNS stimulants such as modafinil or armodafinil can be used to manage sleepiness. With advances in understanding sleep-wake mechanisms, new drugs targeting monoamines such as dopamine/norepinephrine (JZP-110: soliamfetol) or histamine (MK-0249) were developed and are being tested as potential candidates in drug therapy. ■

TABLE 3 Result of EB’s Epworth Sleepiness Scale
Chance of dozing: 0 = none; 1 = slight; 2 = moderate; 3 = high

| | |
|---|-----------|
| Sitting and reading | 3 |
| Watching TV | 3 |
| Sitting inactive in a public place | 3 |
| As a car passenger for an hour without a break | 3 |
| Lying down to rest in the afternoon | 3 |
| Sitting and talking to someone | 2 |
| Sitting quietly after lunch without alcohol | 3 |
| In a car, while stopping for a few minutes in traffic | 0 |
| Total score | 20 |

Note: the total score confirmed subjective excessive daytime sleepiness; an ESS score of 11 or higher is considered to be indicative of excessive daytime sleepiness.

EXCESSIVE SLEEPINESS IN OSA MAY BE MORE THAN AN AIRWAY ISSUE

Evidence suggests that excessive sleepiness (ES) may result from neuronal injury caused by obstructive sleep apnea (OSA).

In animal studies, chronic intermittent hypoxia and fragmented sleep may impair neuronal wakefulness-promoting regions of the brain.¹⁻³ Structural changes in gray and white matter have been associated with reduced neurocognitive performance and compromised neuronal connectivity in patients with OSA.⁴⁻⁶

Learn more about the emerging science of excessive sleepiness in OSA at ESandOSA.com