



Excessive Daytime Sleepiness and Obstructive Sleep Apnea Syndrome

Kannan Ramar, MD, Christian Guilleminault, MD, BioID*

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Excessive daytime sleepiness (EDS) is a common yet very often neglected symptom. Patients may underreport their sleepiness, either because they are not aware of it or because there are social pressures to deny that it is a problem. EDS is increasingly recognized as an important public health problem, affecting at least 12% to 20% of the general adult population [1,2]. EDS is defined as sleepiness (the urge to sleep) that occurs in a situation when an individual is normally expected to be awake and alert. It is important to differentiate true sleepiness from various forms of tiredness, such as lethargy, malaise, or exhaustion.

Obstructive sleep apnea syndrome (OSAS) is the most common cause of EDS among subjects seen

in sleep clinics [3,4]. It is a serious disorder characterized by sleep fragmentation caused by repeated arousals and disruption of normal sleep architecture secondary to partial or complete closure of the upper airway during sleep [5,6]. In patients with OSAS, EDS results in a high rate of accidents in traffic and work. Patients with OSAS are involved in traffic accidents two to three times more often than the general population [7].

Interestingly, not all patients with OSAS, even moderate to severe OSAS, have daytime sleepiness [8]. In the Wisconsin cohort study, only 15.5% of males and 22.6% of females with OSAS (as assessed by apnea-hypopnea index [AHI] at a rate of five events per hour or more) reported sleepiness on

Stanford University Sleep Medicine Program, 401 Quarry Road, Suite 3301, Stanford, CA 94305, USA

* Corresponding author.

E-mail address: cguil@stanford.edu (C. Guilleminault).

three subjective measures used. A higher percentage of subjects, however, reported sleepiness on at least one of the three measurements used [2]. The complaint of “sleepiness” was the least frequently reported symptom when Chervin [9] conducted an informal questionnaire survey on patients with OSAS; most often patients reported “lack of energy” as the symptom that described their daytime experience. Additionally, a substantial subset of patients who denied the daytime complaints reported a variety of other complaints related to changes in cognitive function, such as impaired short-term memory, reduced capacity to sustain concentration or focus, word-finding difficulties, or a lowered frustration threshold leading to irritability [9].

Pathophysiology of excessive daytime sleepiness in obstructive sleep apnea

Arousals and excessive daytime sleepiness

In normal subjects, brief arousals from sleep produce EDS and impaired daytime performance [10,11]. In subjects with obstructive sleep apnea, arousal from sleep is believed to be an essential mechanism for re-establishing airway patency [12]. The apneic and hypopneic events in OSAS are associated with frequent arousals that lead to sleep fragmentation [12,13], and thereby EDS [14]. Also, arousals can occur without apneas, hypopneas, or hypoxemia, and this leads to the concept of respiratory effort-related arousals. Respiratory effort-related arousals are defined as arousals occurring during and interrupting a succession of loud snores. It has been shown that respiratory effort-related arousals occur mostly in association with a rise in inspiratory effort secondary to increased upper airway resistance, resulting in arousals [6]. Short electroencephalogram (EEG) arousals (defined as detectable lightening of the EEG with alpha and beta waves for 3 seconds or more) were subsequently defined in 1992, as efforts were made to define the minimum degree of sleep disturbance that was needed to result in EDS [15].

Investigators have shown no consistent significant correlations between arousals and EDS [16–19]. A recent study by Goncalves and coworkers [20] showed a stronger correlation between short EEG arousals (as per American Sleep Disorders Association [ASDA] criteria [15]) and severity of OSAS than those previously published, but the polysomnographic measures did not correlate with the subjective measurements of sleepiness. Even when other investigators reduced the length of EEG changes required to define an EEG arousal to 1.5 seconds, it was only minimally better at predicting objective daytime sleepiness [21].

Arousals could be poor correlates of objective EDS for various reasons. First, the reasons for daytime sleepiness could be from many factors other than recurrent arousals, such as sleep deprivation, drugs, xanthines, or cytokines. Second, there is night-to-night variation in sleep apnea severity [22], and a single hospital sleep study may not fully represent what happens normally, because the symptom is a cumulative result of variable sleep fragmentation. Third, approximately 28% of apneas and hypopneas are not terminated by visible cortical arousals [23]. This could be caused by the limitations of visual scoring in detecting all arousals, which might be better appreciated by EEG power spectral analysis [24]; it could be related to the fact that apnea and hypopnea may not necessarily lead to an EEG arousal, but only brain-stem activation without involvement of neuronal network above the thalamus. Further validation is needed to compare this marker with EDS severity. Fourth, integrating EDS with other EEG markers of sleep disruption, like cyclical alternating patterns (CAP) and detection of respiratory cycle-related EEG changes in OSAS subjects [25,26], may improve evaluation of EDS. Finally, subjects may have difficulties recognizing their own degree of sleepiness, as shown in many sleep-deprivation or fragmentation studies, but this is mostly associated with denial of sleepiness.

Apnea-hypopnea index and excessive daytime sleepiness

The severity of OSAS is most frequently gauged by measuring the AHI using the overnight polysomnogram. The AHI is used to reflect the severity of sleep fragmentation, but investigators have not been able consistently to demonstrate an association between AHI and EDS when EDS was assessed by the multiple sleep latency test (MSLT) or other measures [16,17,19,21,27]. Other studies have shown inability to correlate sleep study indices with daytime measures of sleepiness, where the r value rarely rises above 0.4 (ie, less than 20% of symptoms across a sleep clinic population seem explicable on the basis of the sleep study, the primary diagnostic tool).

Slow wave activity and excessive daytime sleepiness

OSAS leads to disruption of normal sleep architecture with deprivation of rapid eye movement (REM) sleep and stages 3 and 4 non-rapid eye movement (NREM) sleep, although their sleep efficiency seems to be unchanged [16,28]. Slow wave activity is considered an objective marker for homeostatic process. It has a broader definition that

includes slow wave sleep stage criteria (including slow waves in stage 2 sleep) and a broader frequency distribution (0.75–4.5 Hz). Heinzer and coworkers [29] showed a decrease in slow wave activity across the night with OSAS patients leading to EDS. Slow wave activity increased after nasal continuous positive airway pressure (CPAP) treatment, but there was a lack of correlation with MSLT posttreatment.

Autonomic activation and excessive daytime sleepiness

Autonomic activation has attracted attention as a potential index to quantify sleep disturbance in OSAS [30] because this method identifies even minor disturbing events that occur without visible EEG arousals [31]. There was an increase in EDS in one study, as measured by maintenance of wakefulness test (MWT) in normal subjects when autonomic activations were repeatedly induced in the absence of visible EEG arousals [32]. Subsequently, in OSAS patients, Bennett and coworkers [33] described autonomic activations as predictors of EDS by showing a significant correlation between the autonomic activation index and pretreatment objective sleepiness, and between the autonomic activation index and nasal CPAP responsive objective sleepiness. On the contrary, a recent study [34] showed that activation of brainstem (and thereby autonomic nervous system), without cortical arousal through subthreshold auditory stimulation, did not induce any change in MSLT or subjective sleepiness. Autonomic nervous system changes can be obtained with different types of stimuli; some of them may only involve simple reflexes with relay in medulla and lower brainstem, whereas others are associated with involvement of higher nervous system structures including the cortex. Investigation of autonomic nervous system stimulations, EEG arousal, and importance of autonomic nervous system stimulation necessary to induce sleepiness measured objectively has not been done. To relay only on an autonomic nervous system response to determine cortical arousal is erroneous; some type of EEG analysis is needed.

Hypoxemia and excessive daytime sleepiness

OSAS also leads to repetitive oxygen desaturation, but this variable has not been considered to be of significant importance for EDS [35]. Colt and coworkers [36] showed no change in objective improvement in EDS as measured by MSLT when OSAS patients were treated with nasal CPAP, irrespective of the presence or absence of nocturnal hypoxemia. Their results lend further support to the hypothesis relating EDS to sleep fragmentation. Additionally, many patients with COPD or other

lung diseases who present with chronic hypoxemia, which may tend to be more severe during rapid eye movement sleep, showed no correlation with EDS.

Snoring and excessive daytime sleepiness

Snoring is also associated with EDS, although it could simply be a marker for obstructive sleep apnea. Young and colleagues [2] found that snorers with respiratory disturbance index ≤ 5 were substantially more likely to report EDS than were non-snorers with respiratory disturbance index ≤ 5 . Subsequent work by Gottlieb and coworkers [37] showed a significant association between snoring and sleepiness that was independent of the association between AHI and sleepiness. Snoring may be an independent cause of excess sleepiness, through mechanisms that remain to be elucidated [6]. In the recent past studies of snorers were performed with nasal cannula and pressure transducer, and with esophageal pressure. It was shown that these subjects presented with upper airway resistance syndrome when appropriately investigated, but this syndrome is not presented here.

Cyclic alternating pattern

CAP is formed by electrocortical events that recur at regular intervals in the range of seconds during NREM sleep [Table 1] [25]. These events are clearly distinguishable from the background EEG rhythm as abrupt frequency shifts or amplitude changes. Two phases (A and B) are present that are part of a CAP cycle and recur within 2 to 60 seconds [see Table 1]. When neither of the phases (A and B) is identifiable, sleep has reached a new stable state [38]. Phase A is identified by transient events typically observed in NREM sleep. It includes EEG patterns of higher voltage; slower frequency; and faster lower voltage than the background EEG (with an increase in amplitude by at least one third compared with the background EEG). It is an activation phase lasting 2 to 60 seconds. Phase B follows phase A; it is the interval between two phases A with duration of 2 to 60 seconds, and has been defined by decreased EEG amplitude with EEG evidence of stages 1 to 2 NREM. Phase A has been subdivided into three subtypes. Subtype A1 is marked by a predominance of synchronized EEG activity and less than 20% of desynchronization of the EEG (fast frequency and low amplitude), such as delta bursts, K complex sequences, vertex waves, and polyphasic bursts (of slow and fast EEG rhythms). Subtype A2 is scored in the presence of 20% to 50% of desynchronized EEG activity with a predominance of polyphasic bursts. Subtype A3 is scored when at least 50% of the EEG activity is comprised of low amplitude fast rhythms, such

Table 1: Summary of cyclic alternating pattern phases

CAP phase	Characteristics
Phase A	2–60 seconds Transient events EEG patterns of higher voltage, slower frequency, and faster-lower voltage than the background EEG (increase in amplitude by at least one third)
Subtype A1	Predominance of synchronized EEG activity <20% desynchronization of EEG activity Delta bursts, K complex sequences, vertex waves, and polyphasic bursts
Subtype A2	20%–50% of desynchronized EEG activity Predominance of polyphasic bursts
Subtype A3	≥50% of desynchronized EEG activity Comprised of low-amplitude fast rhythms K-alpha complexes, ASDA-defined arousals, and polyphasic bursts
Phase B	2–60 seconds Interval between two phases A Decreased EEG amplitude with EEG evidence of stages 1–2 NREM

Abbreviations: ASDA, American Sleep Disorders Association; CAP, cyclic alternating pattern; EEG, electroencephalogram; NREM, non-rapid eye movement.

as K-alpha complexes, ASDA-defined arousals, and polyphasic bursts [25].

The use of ASDA short EEG arousals and CAP scorings is increasingly becoming a popular way to evaluate sleep structure unlike the simple sleep staging evaluation based on at least 15 seconds out of one 30-second epoch that is currently being done using the Rechtschaffen and Kales method of scoring. CAP is a condition of NREM sleep instability [25].

Patients with OSAS have increases in CAP rate (>80% at the expense of non-CAP) with apneas and hypopneas usually occurring during phase B. Sleep fragmentation is associated with a significant enhancement of CAP phase A, especially A3 (that correlates strongly with ASDA EEG arousals), and more than 90% of the respiratory events are noted during CAP [39].

The enhanced resolution offered by the CAP, non-CAP perspective can shed light on the complex

interactions between arousal rhythmicity, apneas-hypopnea, sleep disruption, and thereby its role in EDS and the effects of calibrating CPAP to the previously mentioned end points [40]. Further studies are required to explore the advantages of this sleep scoring approach in diagnosis and clinical management of OSAS patients with EDS, including nasal CPAP calibration.

Respiratory cycle-related EEG change

Respiratory cycle-related EEG change is a quantification of computer-based signal analysis that detects subtle cortical responses (otherwise not detected by visual inspection) caused by increased work of breathing in sleep-disordered breathing subjects that might otherwise not be picked up during the nonapneic or hypopneic respiratory cycles. Using this method, Chervin and coworkers [41] showed that in subjects with sleep-disordered breathing the tendency for sigma (13–15 Hz) electroencephalographic power to vary with each respiratory cycle predicted next-day sleepiness as measured by the MSLT. Further investigation is necessary for complete validation of this method.

Measures of excessive daytime sleepiness

Many studies have indicated the difficulty of subjectively recognizing and objectively quantifying sleepiness. Patients and physicians have difficulty recognizing EDS; such terms as “fatigue” and “tiredness” are used interchangeably with EDS by the patients and mistakenly classified by physicians as depression and chronic fatigue syndrome [42]. Table 2 shows a summary of objective and subjective tests currently used in evaluating EDS.

Objective measures

Normally, the initial step in investigating the etiology of EDS is the performance of the overnight polysomnogram test, which can confirm sleep-related breathing disorders. This also helps to rule out other disorders that can potentially cause EDS.

Multiple Sleep Latency Test

As subjective measures of sleep were being formulated, objective measures of sleep were being finalized in 1977 with the advent of the MSLT [43]. This test is administered the day after an all-night polysomnogram to ensure that sleep deprivation does not confound the results. Sleep latency is measured during naps taken at four to five different times during the day. The MSLT is thought to measure physiologic sleep tendency in the absence of alerting factors, with the tendency to fall asleep (decreased sleep latency) increasing as physiologic sleepiness increases. Although the

Table 2: Objective and subjective tests used in assessment of EDS in patients with OSAHS

<i>Objective measures of EDS</i>	
Multiple Sleep Latency Test	<p>Developed in 1977</p> <p>Measures sleep latency in the absence of alerting factors</p> <p>Measured using EEG during four to five naps taken at different times during the day</p> <p>Used as a standard test to evaluate objectively for daytime sleepiness</p> <p>May be affected by the amount of sleep before the test</p>
Maintenance of Wakefulness Test	<p>Developed in 1982</p> <p>Meant to address shortcomings of MSLT</p> <p>Measures ability to function and maintain alertness in common situations of inactivity</p> <p>Measured using EEG during four to five set intervals throughout the day</p> <p>Has similar shortcomings to MSLT</p>
Oxford Sleep Resistance Test	<p>MWT test without EEG monitoring</p> <p>Measures sustained attention and reaction time</p> <p>Patients respond to a light-emitting diode device</p> <p>Lasts 40 minutes and may be repeated up to four times between the 08.00 and 17.00 hour</p> <p>Looks at behavioral lapses, but misses short sleep segments indicated by decreased alertness</p> <p>Sensitive to motivation</p>
Psychomotor Vigilance Task	<p>Measures reaction time</p> <p>Lasts 10 minutes</p> <p>Can be administered at different times of day; there is a circadian modulation of results</p> <p>Sensitive to motivation</p>
<i>Subjective measures of EDS</i>	
Epworth Sleepiness Scale	<p>Developed in 1991</p> <p>Self-administered questionnaire</p> <p>Eight items are rated on a Likert scale from 0 (never) to 3 (high chance), regarding patient's likelihood to doze in sedentary conditions</p> <p>The total of the responses is the Epworth score, which can range from 0–24</p>
Stanford sleepiness Scale	<p>Measures patient's perception of sleepiness over time</p> <p>Seven-point scale of equal intervals measuring subjective sleepiness from being very alert to excessively sleepy</p> <p>Requires collection of many data points during 1 day</p> <p>Measures sleepiness at a single point in time</p>
Karolinska Sleepiness Scale	<p>Investigates the instantaneous degree of sleepiness</p> <p>9 point scale (1=very alert to 9=very sleepy)</p> <p>Measures patient's perception of ability to stay awake or fight sleep</p> <p>Require collection of many data points during 1 day</p> <p>Measure sleepiness at single day in time</p> <p>Investigates the instantaneous degree of sleepiness</p>

Abbreviations: EEG, electroencephalogram; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test.

MSLT is still used as a standard test to evaluate EDS objectively, the validity of this test was never assessed using a large sample of subjects, and questions have been raised as to whether this test should be considered the gold standard in testing for EDS [44]. Also, it has been shown that the amount of prior sleep affects MSLT [45], and thereby the recommendation of performing actigraphy to ensure

that prolonged sleep restriction did not occur before testing has been made, not only for MSLT but for all tests of daytime alertness. Despite its critics, MSLT is still the most documented test of objective daytime alertness, and the only test that can suggest other etiologies for EDS.

When subjects with OSAS were compared with controls, there was significant overlap in mean

sleep latency values on the MSLT, but the overall results showed 7.2 ± 6 and 12.8 ± 4.1 , respectively, which was about 1 to 1.5 standard deviations less than the mean for normal controls [46,47], indicating that the routine use of MSLT to assess EDS secondary to OSAS may not always contribute significantly in diagnosis or evaluating response to treatment for OSAS. The MSLT showed lower mean sleep latency values in subjects with severe OSAS. EDS secondary to severe OSAS was significantly related to the amount of stage 1 NREM during the night, however, and not to scored sleep fragmentation when using Rechtschaffen and Kales sleep staging [16]. Also, no significant relationship was found between the number of abnormal breathing events (that include more than AHI and has been called respiratory disturbance index) and the results of the MSLT [16,17]. Results were better with the use of short ASDA arousals, and much better with the sigma respiratory cycle-related EEG changes scoring as studied by Chervin and coworkers [41]. Further investigations are needed using the more advanced sleep scoring techniques.

Maintenance of Wakefulness Test

MWT was developed in 1982 [48]. This test measures the ability of the subject to stay awake and thereby their ability to function and maintain alertness in common situations of inactivity; it considers a different function than MSLT. Despite this test being often used currently for medicolegal decisions, it also has shortcomings as the MSLT.

Very few studies have examined the factors associated with MWT sleep latency. Although a recent study of subjects with mild to moderate OSAS found age, previous sleep disorder history, and hypoxemia during the night as independent predictors for MWT sleep latency, respiratory variables (eg, AHI) were not independent predictors [33,49]. The study was vague in showing associations between MWT score and potential predictor variables. Also, there was a discrepancy between the MWT and Epworth Sleepiness Scale (ESS) scores for many of the subjects tested [49,50], but ESS has been shown to explore a different domain than MWT. Although some investigators found that whereas MWT latencies tended to be shorter for patients with severe OSAS, there was only a weak relationship between apnea severity and MWT scores [18,50]. Further studies are needed to assess the reliability of MWT in subjects with OSAS.

The Oxford Sleep Resistance Test is an MWT without EEG monitoring: it uses a light-emitting diode device placed at eye level 2 m away from the subject and asks the subject to respond each time the diode flashes [51]. The test lasts 40 minutes and may be repeated up to four times between

the 08:00 and 17:00 hour. As with the following test, it looks at behavioral lapses, but misses short sleep segments indicated by a decrease in alertness. All tests based on lapses have this problem and underscore brief sleep segments. The fact that this test requests motivation to perform from subjects is also a drawback because absence of EEG cannot dissociate real lapses from motivational lapses.

Psychomotor Vigilance Task

Performance tests have also been used frequently to evaluate sleepiness. The most common ones are simple reaction time tests, such as the Psychomotor Vigilance Task, which was standardized to be performed with little training and takes only 10 minutes per session. The test has been administered at different times of day because there is a circadian modulation of results. Different programs perform automatic analysis of the tests and evaluation of the standard deviation of the response time has been indicated as one of the sensitive calculations [52]. No good correlation with the AHI has been shown.

Subjective measures

Epworth Sleepiness Scale

ESS was developed in 1991 as a tool for subjective assessment of EDS [53]. Eight items are rated on a Likert scale from 0 (never) to 3 (high chance) regarding their likelihood to doze in sedentary conditions, and the total of the responses is the Epworth score, which can range from 0 to 24. The validity of the scale was established by correlating it with the gold standard test for EDS, the MSLT; however, the association between the two was weak and the number of subjects was low [53–56]. Additionally, there was no strong association between ESS and OSAS. These associations were measured in studies of smaller sample size. In a study involving a large sample from the Wisconsin Sleep Cohort Study, Punjabi and coworkers [57] described a moderately strong and independent association between ESS and MSLT. Subjects with ESS in the intermediate [6–11] and highest quartiles (≥ 12) had a 30% and 69% increased risk for sleep onset during MSLT, respectively, compared with the lowest quartiles (≤ 5). This study also revealed a dose-response relationship between self-reported sleep duration and MSLT, with individuals reporting less than 6.75 hours of sleep having a 73% increased risk of sleep onset during MSLT compared with individuals reporting more than 7.5 hours of sleep.

Bennett and coworkers [58] found that subjective sleepiness (ESS) correlated more closely with health status (quantified with the Short Form-36 questionnaire) than objectively measured sleepi-

ness with either MSLT or MWT. This is probably because the ESS and Short Form-36 are both subjective measures, and both quantify symptoms in the recent past. In contrast, measures of objective sleepiness quantify sleepiness during a single day. Inconsistent and weak correlations between sleepiness and health status emphasize that there is more to the symptom complex of OSAS than just falling asleep.

Stanford Sleepiness Scale

The Stanford Sleepiness Scale is a seven-point scale of equal intervals measuring subjective sleepiness from being very alert to excessively sleepy [59]. This scale was well validated by two studies, again with small sample size [60,61]. It has fallen out of favor, however, because it is harder to administer; requires collection of many data points during one day; measures sleepiness at a single point in time (ie, it only investigates the instantaneous degree of sleepiness in contrast to the ESS, which seems to measure a general longer perception of presence of sleepiness by the patient); and does not always correlate with the MSLT [62].

Other subjective scales, like the Karolinska Sleepiness Scale, are not used regularly because they have problems similar to the Stanford Sleepiness Scale, requiring effort to administer, and measuring instantaneous sleepiness on one particular day.

Although there has been a failure to find consistent evidence of a relation between daytime sleepiness and OSAS, it has been suggested that sleepiness may be related to different factors. Also, important limitations of the existing research should be considered. First, the MSLT and the MWT may not adequately reveal diurnal impairment in sleepy patients and they do not strongly correlate with the subjective estimation. One factor may be that the field covered by each test may be different from the other, and the tests may not ever be comparable, as indicated later. Second, objective tests of sleepiness seem to measure a combination of sleep propensity and underlying arousal and studies are still needed systematically to evaluate motivational and psychologic factors that could affect the objective tests. Third, a decrease in mean sleep latency in the MSLT may occur even when the subjects rated themselves as alert, suggesting that subjective estimation measures different aspects of sleepiness [63–66].

There are other possibilities to consider as to why some OSAS patients have EDS, whereas others do not. First, subjects may not be able readily to perceive their daytime sleep propensity because they may have had slow adaptation. Second, nonsleepy patients may have an innate increased sleep onset threshold or a greater level of brain activation.

Third, a differential, patient-specific detrimental effect on cognitive function may exist and the capacity to elucidate other less obvious deficits with present tests is simply lacking. Neither objective nor subjective measures of alertness currently characterize the phenomenon of sleepiness with complete accuracy.

Consequences of sleepiness

Excessive sleepiness is recognized as an important public health problem. In patients with OSAS, sleepiness can impair social function and can have a major impact on the ability to carry on daily life activities, affecting quality of life (QOL), job performance, and contributing to motor vehicle accidents.

Quality of life

Impaired QOL is common among patients with OSAS [67–70]. These patients may experience moodiness, anxiety, lack of motivation, and compromised performance in social function, all of which may contribute to a lower QOL. EDS is a major symptom of OSAS, and seems to be related to a decreased QOL for patients with OSAS [71]. Although the progression of EDS symptoms and their effect on QOL have not been investigated in detail, and although it has been suggested that QOL is dependent on the patient's depressive status, several studies examining the association between EDS and QOL have shown that EDS, whether measured subjectively or objectively, was associated with decreased QOL [72,73]. Sleep deprivation can also lead to endocrine and metabolic changes associated with diabetes and weight gain; it is not uncommon for obese patients to have lower sleep efficiency and increased daytime sleepiness as measured by ESS [74], but these symptoms get worse when associated with OSAS. A large epidemiologic study of overweight subjects found that those with symptoms of OSAS reported poorer perceived health, lower economic income, increased odds of having had psychiatric care, multiple divorces, and impaired work performance compared with overweight subjects without symptoms of OSAS [75].

Functional impairments are normally mediated by symptom severity. QOL scales, such as the medical outcomes study Short Form-36, have been used to study the effect of OSAS on overall health. The Short Form-36 evaluates physical, emotional, and social functions; pain; general health; vitality; and mental health. This scale has revealed considerable impairments in samples of patients with OSAS, with vitality being most affected indicating a greater affect of OSAS on sleepiness [76].

Cognitive decline

Reports have described an association between OSAS and cognitive decline, and some have implicated EDS as the primary component of this association [77]. Patients with EDS secondary to OSAS can suffer from poor concentration and memory disturbance, making it difficult to function productively and efficiently on a day-to-day basis. A recent study showed two thirds of new patients with OSAS reported difficulties in work efficiency and performing new tasks [78]. Another study of industrial workers described negative effects of EDS on workers' well-being including higher rates of work accidents, less job satisfaction, and higher drug usage [79]. Patients may try to compensate for daytime sleepiness with behavioral adjustments, such as napping or taking stimulants.

Motor vehicle accidents

Also of major concern is sleepiness as an important cause of motor vehicle accidents, which often result in injury and death and cost billions of dollars each year. Habitual sleepiness while driving caused by a chronic condition, such as OSAS, occurs more frequently in middle age, whereas younger drivers more commonly experience sporadic sleepiness caused by sleep deprivation, alcohol, or drug abuse [80]. Drivers with OSAS may be two to seven times more likely to have a motor vehicle accident compared with normal drivers [81,82]. Research using the Psychomotor Vigilance Task to study reaction time and response in subjects with sleep-disordered breathing has shown lapses, slow response time, and variability in response time comparable with actions of sleep-deprived or alcohol-impaired subjects [52]. Interestingly, although drivers may know when they are sleepy, they cannot reliably predict when they have become impaired [83,84].

Previous studies have found that sleepiness measured by the ESS or sleep latency measured by the MSLT does not predict which drivers with OSAS will or will not have a motor vehicle accident [81,85–89]. Additionally, neither of these tests measure sleepiness while driving, making it difficult to measure a possible association of EDS with automobile accident risk. For these reasons it has been suggested that asking about excessive sleepiness while driving rather than asking about overall sleepiness may suggest which breathing-disordered sleepy drivers are at higher risk of having a motor vehicle accident [80]. Currently, there are no clinical methods that identify which drivers with OSAS are at higher or lower risk of causing an accident [90]. The ability subjectively to assess a patient's ability to drive safely may be complicated if the patient is reluctant to admit struggling with daytime sleepi-

ness in fear of losing one's license. This may lead to difficulties with assessment of EDS based on subjective measures. A physician responsible for the care of a patient with OSAS should address the issue of safe driving; however, despite the advice of a physician, patients with excessive sleepiness may often continue to drive in traffic, highlighting the importance of preventive efforts that focus on increasing the awareness of the dangers of sleepiness behind the wheel.

Obesity, sleepiness, and obstructive sleep apnea

Many obese patients suffer from OSAS and EDS. It has even been suggested that there is a continuous interaction between weight increase, OSAS, and sleepiness. Any subject over 25 kg/m² is considered overweight, and any small increase in body mass index above 2 standard deviations of the norm (ie, above 25 kg/m²) increases the chance of abnormal breathing particularly when supine and during REM sleep when weight distribution is android (ie, involving the abdomen). There is also occurrence of disturbances of metabolic and inflammatory factors that may again impact breathing during sleep. Such impairments may have a low key effect on sleep initially, but may have negative feedback on alertness, and may lead to sleep fragmentation and change in normal daytime activity levels with feedback on activity, food intake, and ultimately on weight. Presence of feedback loops with negative impact on both weight and alertness have been suggested; however, further research on these feedback loops with progressive worsening of signs and symptoms is needed.

Treatment options for excessive daytime sleepiness caused by obstructive sleep apnea syndrome

Nasal continuous positive airway pressure

Nasal CPAP therapy has emerged as the primary treatment for OSAS. It works either by increasing the intraluminal pressure in the pharynx, and thereby providing a mechanical pneumatic stent of the upper airway [91,92], or by increasing the lung volume, which then mediates the upper airway stabilizing effect [93] (and probably both factors are active). When used properly and consistently CPAP is the treatment of choice for symptoms of EDS secondary to OSAS. There is still debate, however, regarding the efficacy of this modality in treating symptoms of EDS. Currently, Medicare covers CPAP devices for patients with an AHI of ≥ 15 , or patients with sequelae of OSAS and an AHI of 5 to 14. Such sequelae include

EDS, impaired cognition, hypertension, coronary artery disease, cerebrovascular accident, mood disorders, and insomnia.

Wright and coworkers [94] did a systematic review of the literature in 1997 looking at the treatment of OSAS with CPAP. Although the review consisted of studies that were often poorly designed (except for one randomized controlled trial with a small sample size) with nasal CPAP and control groups often not comparable at baseline, they still strongly suggested that CPAP may be effective in reducing EDS. There have been several randomized controlled trials, including sham CPAP as placebo-control, that consistently show that in patients with symptomatic mild to severe OSAS with daytime sleepiness, CPAP reduced subjective and objective measures of EDS and improved QOL [95–106]. Patients with OSAS who are experiencing EDS may benefit more from treatment with nasal CPAP than patients without EDS. Interestingly, when Barbé and coworkers [8] looked at patients with severe OSAS (with AHI >30 per hour) with no daytime sleepiness, they found 6 weeks of nasal CPAP treatment had no significant effect on objective and subjective measures of daytime sleepiness. The lack of substantial improvement in daytime sleepiness could be related to a “floor effect”; the score was already low at baseline and there is little room for it to decrease further. The results of this study may not be reliable because of the small sample size. A recent meta-analysis was performed by Patel and coworkers [107] looking at all published randomized controlled trials of nasal CPAP in patients with OSAS. They specifically addressed the effects of nasal CPAP on subjective and objective sleepiness, and found that CPAP therapy across diverse populations of patients with OSAS resulted in significant improvement in subjective (decreases ESS by 2.94 points) and objective (increases sleep latency by 0.93 minute) measures of sleepiness. Effectiveness of nasal CPAP for OSAS patients with EDS may be overestimated if negative trials were unpublished and thereby not included in this meta-analysis.

Compliance is an issue in administering nasal CPAP; patients need to maintain long-term use of the treatment for it to be effective. Kribbs and coworkers [108] reported that just one night without treatment was sufficient to reverse improvements, despite a reduced AHI compared with pretreatment levels. Although high success rates with long-term use of nasal CPAP [109] have been reported, most of these studies were subjective, and described rates based on patient self-reports. Later objective studies used time clocks built into CPAP machines to record use and found that rates of CPAP use are actually lower [110,111] and often irregular,

rarely meeting prescribed levels [108,112]. There are few long-term objective studies on nasal CPAP compliance.

There are several reasons for intolerance of nasal CPAP. First, patients using CPAP frequently report nasal discomfort. Often little effort is made to treat the nose, impaired by deviated septum and very commonly enlarged nasal inferior turbinates. Radiofrequency treatment of the nasal turbinates and aggressive treatment of nasal allergies help to decrease nocturnal disruption and residual sleepiness in OSAS patients. Second, problems have been encountered in calibrating nasal CPAP, as described by Thomas [40]. Calibration of nasal CPAP is performed by looking at the nasal flow curve, which does not detect the presence of small sleep disruptions that can only be seen with CAP scoring. Subsequently, inadequate treatment of OSAS with nasal CPAP slowly leads to the re-appearance of complaints of tiredness and sleepiness. This is particularly true with autotitrating equipment: this equipment has several drawbacks. First, it is often set up with a very wide range of pressures (eg, 4–20 cm H₂O) and such settings increases the risk of overshoot of pressure and thereby arousals. Second, it reacts slowly to the need for increasing pressures and this fragments sleep. Last but not least, OSAS is associated, at least in a certain number of patients, with permanent neurologic lesions in the upper airways that have been well demonstrated since the early 1990s [113,114]. Treatment with nasal CPAP or bilevel CPAP never cures the permanent lesions. Slow evolution of these lesions over time related to the presence of local neuropathy is expected, and subsequently there is a need to reset pressures at higher levels. This was found in one of the authors' studies exploring patients with clear OSAS at entry (AHI ≥30 events per hour) [115]. This finding indicates the need to recalibrate nasal CPAP on a regular basis (probably every 2 years if no symptom occurs before). Recalibration should be done after interruption of CPAP for 1 night and even more so for 2 or 3 nights. This leads to increased nocturnal sleep disruption, initially demonstrated with CAP scoring during the night, and allows for better recalibration of the machine. Permanent neurologic lesions alone can lead to persistence of EDS, as explained later.

Residual daytime sleepiness

Even with regular use of nasal CPAP, residual daytime sleepiness may persist in patients with OSAS, and reasons for this are not always clear. Many patients who use nasal CPAP regularly may experience insufficient sleep syndrome, which leads to

cumulative partial sleep loss and impaired alertness and performance during the day [116].

Interruption of nasal CPAP for 1 night and even more so for 2 or 3 nights before recalibration leads to increased nocturnal sleep disruption and re-appearance of sleepiness. Patients using nasal CPAP for only part of the night experience abnormal breathing when CPAP is not being used. Appropriate nocturnal nasal CPAP usage is often described as at least 4 hours per night, but there is no evidence that partial usage of CPAP during the night is sufficient to avoid re-appearance of sleepiness in the long run. There is no data supporting the notion of complete treatment of sleepiness with usage of nasal CPAP for only a part of sleep, and thereby recommending a minimum cutoff point of time of usage is speculative.

Persistence of residual EDS despite regular nasal CPAP use and appropriate calibration with monitoring of sleep EEG may also be seen. One study found an association between abdominal obesity and persistence of EDS [117]. Nasal CPAP is a poor treatment of chest bellows syndrome, related to clear abdominal obesity, particularly during rapid eye movement sleep. In this case, bilevel PAP gives a better approach, but residual sleepiness also has been seen with bilevel PAP. Two hypotheses have been raised in this regard. First, the potential association of obesity with EDS: obesity leads to metabolic and inflammatory changes that in themselves have an impact on sleep; however, good studies are lacking to support this plausible hypothesis. Second, the presence of central nervous system lesions that lead to persistence of EDS. Gora and coworkers [118] presented some preliminary data indicative of abnormal evoked potential during the NREM sleep in OSAS patients. A more definitive study was performed by Afifi and coworkers [119], which clearly showed the absence of evoked responses to inspiratory occlusion stimuli during NREM sleep. The absences of these responses may be related to local neuropathy, but secondary neuronal degenerative evolution also could have happened. Another possibility is that repetitive hypoxemia, arousals, and cerebral blood flow changes associated with sleep-disordered breathing for years could account for these permanent central nervous system changes, particularly in an individual with a certain genetic background. For example, the presence of the APOE-4 gene is considered to be a risk factor for neurodegenerative disease, and is currently shown to be present in a series of OSAS patients [120].

Sleepiness may also be indicative of other risk factor associations, such as a coexisting undiagnosed sleep disorder, and antihypertensive or other drug use. Also, as studies are looking at the poten-

tial association between obesity and EDS, other causes of EDS apart from sleep disordered breathing should be considered at, such as the association of EDS with mood disorders (eg, depression), metabolic factors like diabetes, and age.

Modafinil

Modafinil, 2-[(diphenylmethyl)-sulfinyl] acetamide, promotes wakefulness and is currently used in treatment of daytime sleepiness in adults suffering from narcolepsy. Use of amphetamine-like drugs for the treatment of EDS secondary to OSAS is limited because of psychiatric disturbances, interference with night sleep, and the addictive nature of these drugs [121]. Alternatively, modafinil is a non-amphetaminic drug that has fewer side effects, does not interfere with night-time sleep, and has lower potential for abuse [122,123].

This drug has no effect on the AHI, but has been shown to reduce objective sleepiness. Six prospective studies report the effects of modafinil on EDS in OSAS patients. Five studies [124–128] have reported the effects of modafinil (200–400 mg/day) on residual sleepiness in subjects with OSAS, despite compliance with CPAP [Table 3]. Across studies, modafinil consistently improved subjective and objective sleepiness, QOL, and vigilance compared with placebo. Dinges and Weaver [129] reported that the frequency of lapses of attention during Psychomotor Vigilance Task performance was significantly decreased, and both the median and slowest reaction times were significantly improved in subjects treated with nasal CPAP and modafinil compared with those treated with nasal CPAP and placebo. It is important to appreciate, however, that most (75%) subjects with severe sleepiness at baseline had multiple sleep latency times of <10 minutes on modafinil, despite effective CPAP and good compliance with therapy. Prescribing modafinil should not lessen the concerns of continued risk for driving-related motor vehicle accidents caused by sleepiness in patients with OSAS.

Adverse events attributed to modafinil include headaches, nervousness, and rhinitis (5%–10% higher likelihood than placebo). A 2-week, placebo-controlled study with one dose (400 mg) of modafinil [124] demonstrated that patients using this stimulant had a modest but significant reduction in their nightly usage of nasal CPAP. This negative effect was not found in two other double-blind studies of longer duration [125–127], or in the open-label continuation study [128].

Acute administration of modafinil increases arterial blood pressure and heart rate [126]. With exercise, modafinil intake (300 mg) results in a

Table 3: Randomized studies showing improved outcomes for treatment with modafinil in patients residual EDS despite compliance with CPAP

Study	No. of subjects	Dose/number of days treated	Outcome measures for modafinil group (compared with placebo group)	P-value
Kingshott et al	32	200 mg × 5 d 400 mg × 9 d	Improved alertness as measured by MWT. No significant improvement with ESS or MSLT. FOSQ showed trend of improved vigilance.	0.02
Pack et al	157	200 mg × 7 d 400 mg × 21d	Improved alertness as measured by MWT. Lower ESS score. Longer sleep latency as measured by MSLT (slightly worsened for placebo).	<.001 0.0001 0.021
Heitmann et al	24	300 mg × 2 d	Shorter mean reaction time as measured by vigilance test. Longer mean sleep latency as measured by MSLT.	0.0023 0.0001
Black et al	305	2 groups 200 mg × 84 d (12wk) 400 mg × 84 d (12wk)	68% patients showed overall clinical improvement in both treated groups. Improved alertness as measured by MWT. Lower ESS score. Improved FOSQ score.	<.001 ≤.0001 <.0001 <.001
Schwartz et al	125	(12wk) 200 mg week 1 400 mg week 2 By week 12, 17% of patients were on 200 mg, 19% on 300 mg, and 64% on 400 mg	73% patients showed overall clinical improvement. Improved FOSQ score. Lower ESS score.	0.001 <.0001 <.001

Abbreviations: ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test.

significant increase in mean, systolic, and diastolic pressures and heart rate, compared with placebo. No long-term investigation of cardiovascular outcomes with the use of modafinil has been reported.

In summary, the double-blind, placebo-controlled clinical trials that examined the effectiveness of modafinil in patients compliant with nasal CPAP in treating residual sleepiness found that modafinil subjectively and objectively improved vigilance and sleepiness for as long as 12 weeks. Modafinil, however, does not fully reverse severe baseline sleepiness. It seems that 200 mg daily is as efficacious as 400 mg. There is concern that compliance with nasal CPAP may decrease with modafinil usage [124], and this requires further study. In the interim, patients must be advised of the importance to continue CPAP therapies and physicians must carefully monitor CPAP compliance in this group. The question of the long-term effect of modafinil on the hemodynamic status of OSA patients treated with nasal CPAP remains unresolved. Nevertheless, findings from one study measuring cardiovascular responses to modafinil raise the possibility that modafinil use may increase blood pressure [126]. Careful consideration of an individual patient's

health risks (the risk of motor vehicle accidents compared with the risk of cardiovascular morbidities) is required before prescribing modafinil.

Modafinil may also prove useful in patients with mild OSAS, who often go untreated because of the relatively inconvenient nature of current treatments [129,130]. Although modafinil does seem to enhance alertness, it does not treat the underlying pathophysiology of airway collapse in OSAS and may not be of therapeutic benefit for patients who are not receiving adequate prophylactic treatment for apneas and hypopneas, and may result in serious complications because of long-term OSAS that has gone untreated.

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