

Quality of life consequences of sleep-disordered breathing

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Sleep-disordered breathing occurs in approximately 2% to 4% of the adult population and includes conditions in which patients stop breathing completely (apnea) or have marked reductions in airflow (hypopnea) during sleep. Typical symptoms of sleep apnea include snoring, restless sleep, excessive daytime somnolence, nocturnal enuresis, irritability, depression, memory deficits, inability to concentrate, and decreased alertness. The clinically relevant outcomes of these symptoms include impairment in work efficiency, increased automobile accident rates, and decrements in quality of life. Treatment of sleep apnea, primarily with continuous positive airway pressure, reduces sleepiness and improves mood disturbances, neurocognition, and performance. Traditional measurements of sleep apnea severity do not correlate well with current tests and scales that are used to quantify alterations in alertness, performance, quality of life, or sleepiness. A disease-specific quality of life scale has been developed following patient and physician interviews and literature reviews. The Calgary Sleep Apnea Quality of Life Index is expected to capture aspects of quality of life important to sleep apnea patients, such as cognitive function, performance, and mood, that could be improved with appropriate treatment of sleep-disordered breathing. (J Allergy Clin Immunol 1997;99:S750-6.)

Key words: Sleep-disordered breathing, sleep apnea, quality of life, excessive daytime somnolence

Sleep-disordered breathing describes a broad spectrum of conditions in which individuals have a complete cessation of breathing (apnea) or a marked reduction in airflow (hypopnea) while asleep. It was initially recognized in its most severe form, obesity hypoventilation, or pickwickian syndrome.¹ Patients can suffer from cor pulmonale as a consequence of this rare disorder. At the other end of the spectrum are patients with heavy snoring indicative of increased resistance to airflow through the upper airway during sleep.² In its milder form, sleep-disordered breathing may not lead to obvious side effects, and it is frequently unappreciated by both patient and physician. However, sleep-disordered breathing can lead to a number of medical illnesses and symptoms, thus making it a serious public health problem.³ The most common, and often most debilitating, symptom is excessive daytime somnolence.

By convention apneas and hypopneas are considered clinically relevant if they last a minimum of 10 seconds.⁴ It is not uncommon for apneas to persist for 30 to 60 seconds in some individuals. In general, apneas and hypopneas are classified as central, obstructive, or mixed. Central apneas occur as a result of an absence of neural output from the brainstem's respiratory centers, which leads to a lack of inspiratory effort.⁵ Obstructive apneas result from closure of the pharyngeal airway,

Abbreviations used

AHI:	Apnea-hypopnea index
COPD:	Chronic obstructive pulmonary disease
CPAP:	Continuous positive airway pressure
DADT:	Divided attention driving test
EDS:	Excessive daytime somnolence
EEG:	Electroencephalogram
ESS:	Epworth Sleepiness Scale
MSLT:	Multiple Sleep Latency Test
MWT:	Maintenance of Wakefulness Test
NHP:	Nottingham Health Profile
PGY:	Postgraduate year
PVT:	Psychomotor vigilance tasks
QOL:	Quality of life
SA:	Sleep apnea
SAQLI:	Calgary SA Quality of Life Index
SF-36:	Medical Outcomes Study 36-Item Short-Form Health Survey
SIP:	Sickness Impact Profile
SSS:	Stanford Sleepiness Score

which prevents an inspiratory effort from affecting the flow of air into the lungs.

Although considered physiologically distinct, there is some overlap between these two types of events.⁶ In some circumstances, apneas may initially be central, with no evidence of inspiratory effort. Eventually, respiratory effort commences, but apnea persists because the upper airway is also closed. Conditions contributing to upper airway closure include allergic rhinitis, chronic sinusitis, and physical obstruction. These breathing disturbances are referred to as *mixed apneas*.

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0091-6749/97 \$5.00 + 0 1/0/79131

Central sleep apnea (SA) is an uncommon disorder, compared with mixed and obstructive SA. SA severity is often characterized by the apnea-hypopnea index (AHI), which refers to the number of apneas and hypopneas that occur per hour of sleep. In the literature, commonly used categorical definitions of SA are AHI > 5, 10, or 15. Severely affected individuals can have an AHI that exceeds 100. The SA syndrome is defined as an AHI above a clinically relevant threshold with the presence of excessive daytime somnolence.⁷ In a recent community-based study of working adults, the Wisconsin Sleep Study Cohort, the SA syndrome was observed in 4% and 2% of adult males and females, respectively.⁸

When an apnea or hypopnea occurs, it is frequently accompanied by hypoxemia and hypercarbia of varying degrees. It is not uncommon for some patients to regularly desaturate to levels below 70% and, occasionally, below 60%. Apneas and hypopneas often result in arousal from sleep, which then terminates the breathing disturbance.⁹ Once aroused, the central nervous system can respond appropriately to the partial or complete closure of the pharynx with a brief contraction of the pharyngeal dilating muscles. This restores upper airway patency and permits resumption of airflow, with subsequent reversal of the hypoxemia and hypercarbia. Arousals often last for only 1 to 3 seconds and are not recognized by the patient. Upon awakening in the morning, they often are completely unaware that they aroused several hundred times during the night. Arousals are often accompanied by surges in blood pressure.^{10, 11} It is believed that recurrent arousals, and the consequent sleep disruption, are the cause of many of the daytime symptoms and effects of SA.¹² However, some investigators also believe that hypoxemia plays a role.^{13, 14}

There is often a very poor correlation between the AHI and subjective symptoms, suggesting that the AHI in isolation is not a good indicator of disease severity.^{15, 16} This is not surprising since there are multiple factors that play a role in generating the symptoms that these patients experience. For example, it has been found that some people have increased resistance to airflow in the upper airway during sleep, which is known as the *upper airway resistance syndrome*. They do not have apneas or hypopneas but, nevertheless, have similar symptoms as SA patients, and, indeed, they may respond to standard treatment for SA.¹⁷ In addition to excessive daytime sleepiness, typical symptoms of SA include snoring, restless sleep, nocturnal enuresis, irritability, decreased libido, decreased alertness, inability to concentrate, memory deficits, and fatigue.¹⁸ SA has also been implicated as a factor in the development of depression.¹⁹ Additionally, several investigators have documented deficits in various neurocognitive tasks including memory, attention, and vigilance.¹²⁻¹⁴ To date, there has been relatively little information published on how quality of life is affected by SA.

The standard treatment for obstructive sleep apnea is continuous positive airway pressure (CPAP), which ef-

fectively prevents upper airway collapse, resulting desaturations, and arousals from sleep.²⁰ CPAP has been shown to reduce objective sleepiness, improve mood disturbances, neurocognition, and performance.^{21, 22} In selected patients, successful treatment outcomes also have been obtained with mandibular advancement devices,²³ uvulopalatopharyngoplasty,²⁴ and occasionally with life-style modifications.

EXCESSIVE DAYTIME SOMNOLENCE

SA has been implicated as a cause of numerous daytime symptoms, many of which are the result of chronic sleep disruption. The most common and pervasive symptom is excessive daytime somnolence (EDS). SA and narcolepsy are the two most common medical causes of moderate and severe EDS.²⁵ EDS is a common problem in Western society, with a prevalence rate of up to 5%.²⁶ It is disruptive to afflicted patients, since over half of severely hypersomnolent patients report loss of job or disruption of family life.²⁷ Moreover, it is a significant public health issue, given the association between EDS and automobile accidents.²⁸⁻³⁰ Unfortunately, little attention has been paid to patients who report daytime sleepiness, since it is often passed off as a minor problem in the context of the primary reason for patient referral. In addition to this lack of awareness of EDS among health care professionals and the general public, there are limited methods available to assess the impact of EDS on patients and society as a whole.

Testing may take the form of determining how easy it is for a patient to fall asleep, or, alternatively, how difficult it is for them to remain awake. This type of testing may include both subjective and objective assessments. Two common subjective assessments of sleepiness are the Stanford Sleepiness Score (SSS)³¹ and the Epworth Sleepiness Scale (ESS).³² The SSS is used to record the degree of sleepiness experienced by an individual at a given time and does not necessarily relate to his or her overall propensity to fall asleep. The ESS measures sleepiness as a reflection of a subject's tendency to fall asleep during specific, nonstimulating situations, as assessed over an interval of time. Both have been validated and demonstrate clear differences between subjects and controls.^{31, 32}

In general, an ESS score of greater than 10 is considered indicative of EDS. The ESS is worse in patients with SA and improves following long-term treatment with CPAP.³³ Johns has demonstrated that the ESS score increases with worsening severity of SA. However, although the relationship is statistically significant, the correlation between the AHI and ESS is poor ($r = 0.439$). Thus, traditional measures of SA severity do not adequately capture the impact of the breathing disorder on a patient's life.³⁴

The standard objective measurement of sleepiness is the Multiple Sleep Latency Test (MSLT),³⁵ which involves a series of 20-minute scheduled naps administered over 2-hour intervals for a total of 8 hours. While lying in a darkened room and connected to electroen-

cephalographic (EEG) monitoring, the patient is instructed to try and fall asleep. The time required for EEG-confirmed sleep is recorded and averaged over the five naps and reflects the tendency for a patient to fall asleep. This test has been validated in a number of settings including sleep deprivation, the use of sedative antihistamines, and intrinsic sleep disorders.³⁶⁻³⁸ An MSLT of less than 5 minutes has been associated with performance decrements and unintentional daytime naps or microsleeps.³⁸ A result between 5 and 10 minutes is considered a diagnostic gray area. Normal volunteers score in the range of 10 to 20 minutes. Since the MSLT requires EEG monitoring, it is used primarily in the research setting. Many of the earlier studies evaluating the MSLT utilized mixed populations consisting of patients with SA, as well as other conditions that predispose patients to EDS. More specifically, in the SA setting, it has been consistently demonstrated that patients with SA have abnormal MSLTs and that the application of nasal CPAP will improve MSLT scores. Moreover, in more severe cases, discontinuation of CPAP for as little as one night, may result in worsening MSLT scores and increased symptoms of EDS.³⁹ Mitler et al.⁴⁰ developed the Maintenance of Wakefulness Test (MWT), a variant of the MSLT, in which the patient is instructed to stay awake while sitting in a darkened room for 40 minutes. The time required until EEG-confirmed sleep is recorded. Although the correlation between the MWT and MSLT is statistically significant, there is considerable variability between the two tests.⁴¹ Unlike the MSLT, the MWT is believed to better correlate with alertness rather than sleepiness, furthering the observation that sleepiness does not always imply decreased vigilance.

DEPRESSION

SA has been shown to be associated with depressive symptoms in many studies, although this is not a universal finding. Most studies have been cross-sectional and have involved selected and, therefore, biased samples of patients to establish this association. Kales et al.⁴² observed depression in 56% of 50 patients with SA. However, these patients had severe SA, and tracheostomy was recommended for treatment. Therefore, they are not representative of the majority of patients with SA. Millman et al.⁴³ demonstrated improvement in depression scores using the Zung Self Rating Depression Scale after CPAP treatment.⁴³ These results may have been confounded by several items on this scale that might be directly influenced by SA (e.g., fatigue, sleep disruption, task performance), indicating that the results are not a direct reflection of psychopathology in these patients. A small study of seven patients who completed the Profile of Mood States questionnaire before and after CPAP demonstrated that two of six mood factors (depression and fatigue) as well as the Total Mood Disturbance Score improved significantly with treatment.⁴⁴ Reynolds et al.,⁴⁵ in a study of 25 SA patients,

determined that 25% had a history of major depressive episodes or chronic intermittent depression.

Cassel⁴⁶ did not find any personality changes in 76 SA patients who completed a personality inventory. Lee⁴⁷ studied 60 SA patients and found none that fulfilled the DSM III-R criteria for depression. We administered the 12-item version of the General Health Questionnaire⁴⁸ to a consecutively referred sample of 180 patients who were all investigated with polysomnography.¹⁵ Using a cutoff of three to define patients with depression, there was an equal percentage of patients (40%) in both the SA and non-SA groups with depression, suggesting that the breathing disturbance during sleep and depressive symptoms were not causally related. In a more robust study design that involved a placebo-controlled crossover study of the effects of CPAP in 32 SA patients, Engleman et al.²² identified 10 and 8 patients with anxiety and depression, respectively, while receiving placebo using the Hospital Anxiety and Depression Scale. These numbers were reduced to four patients with anxiety and four patients with depression while receiving CPAP. Using the General Health Questionnaire 28-item version, a reduction in the number of depressive cases from 11 to 5 was observed with treatment.²² The relationship between SA and depression is undoubtedly multifactorial. There are certainly symptoms that overlap and thus confuse the exact nature of the relationship. Nevertheless, a large percentage of patients that are referred to sleep-disorder clinics for possible SA have symptoms of depression, which, at least in some, are improved with treatment of sleep-disordered breathing.

NEUROCOGNITIVE DYSFUNCTION AND PERFORMANCE IMPAIRMENT

Numerous studies have evaluated SA patients for neurocognitive dysfunction, each using a battery of neuropsychological tests. A clear pattern of deficits has not emerged.^{13, 14, 49-54} By and large, investigators have used different methodologies, different control populations, and probably different recruitment strategies to obtain their study population. Consequently, findings often differ from study to study. A comprehensive review of these studies is beyond the scope of this article. In most studies, a battery of tests are used to evaluate a small number of patients, and only a few positive results are observed, which generally do not correlate well with the AHI. Significance values are not always corrected for multiple comparisons in these studies, and as a result, it is difficult to discern a causal relationship between SA and neurocognitive deficits. In general, deficits in verbal memory in SA patients are found more commonly than deficits in nonverbal memory. One or more studies have found deficits in the areas of verbal function, visuospatial organization, visuomotor coordination, attention, verbal IQ, and performance IQ. In a placebo-controlled, crossover study of CPAP treatment, Engleman et al.²² found that there were no changes in verbal fluency or memory between placebo and active-treatment periods. There were, however, small but statistically significant

improvements in vigilance (Steer Clear), mental flexibility (Trailmaking B time), and coding speed (digit symbol substitution). They also found learning effects on repeated tests of cognitive function, suggesting that uncontrolled studies of before and after comparisons of treatment on cognitive function can be misleading.

Based on many previous studies, it would be expected that EDS plays a significant role in the cognitive impairment exhibited by some SA patients. Recently, considerable interest has been focused on performance, attention, or vigilance testing, which is ultimately of more relevance to SA patients than standard batteries of neuropsychological tests. Alertness, vigilance, and performance readiness are all terms used to describe the ability of persons to remain awake well enough to perform specific tasks. Vigilance testing and performance testing, terms that are often used synonymously, refer to different methods of measurement. The correlation between a simple test of vigilance and a more complex performance task may not be high.⁵⁵ Similarly, there may be a poor correlation between measures of daytime somnolence and degree of vigilance impairment.^{41, 56} Individuals are able to compensate for EDS to varying degrees. Interest level, motivation, test duration, proficiency level (sometimes referred to as *practice effect*), and circadian rhythms can all influence test results. When individuals are engaged in interesting tasks, they are able to maintain performance for significantly longer periods.⁵⁷ Similarly, incentives, such as monetary awards, result in longer maintenance of vigilance than nonremunerated controls.⁵⁸ The duration of the test also is of great importance. Following two nights of sleep deprivation, subjects have been shown to maintain normal problem solving for 10 minutes; however, by 50 minutes they show obvious decline.⁵⁹ Circadian rhythm has an impact on performance testing, and because it has an interactive effect with proficiency level, results must be interpreted with caution.⁶⁰ Since proficiency level influences performance on subsequent tests,⁵⁵ patients should not be familiar with the required tasks, and interpretation of follow-up tests must take the practice effect into account. Practice effect can be present in tests of simple, repetitive tasks as well as in those of complex social interactions. This has been demonstrated in a comparative study of sleep deprivation in PGY-1 and PGY-2 surgical residents.⁶¹

At the simplest level, vigilance testing involves a simple motor task to be performed when a specific cue, either visual or auditory, is given. Psychomotor vigilance tasks (PVT) involve measuring average response times of a subject to pressing a button in response to a repetitive visual stimuli over a short test period.⁶² The use of PVT has been validated in the setting of sleep deprivation as well as in SA patients studied before and after receiving CPAP.^{39, 63} Other variations on this type of test include the Steer Clear system, which tests a subject's ability to press a key to avoid hitting objects on a computer-projected two-lane highway,⁶⁴ or the Wilkinson Additions Test, which uses problem solving.⁶⁵

As in all areas of medicine, the final objective of any test is to detect clinically relevant outcomes. In the case of EDS, this would represent impairment in work efficiency, increased accident rates, or decrements in quality of life. Automobile accident rates represent the best studied facet of EDS outcomes research, and thus serve as a useful paradigm in illustrating the difficulties in developing meaningful assessment variables for patients with EDS. It has become apparent that patients with EDS, and in particular those with SA, have a higher rate of automobile accidents than the normal population.^{28, 29} Consequently, identifying high-risk individuals is of critical importance from both a public health and a medical-legal perspective.²⁵ Although the relationship between SA and increased risk for motor vehicle accidents is generally accepted at the individual level, there is considerable variability between driving performance and traditional measures of sleepiness (ESS, MSLT) or SA severity (AHI).^{55, 56} Similarly, while vigilance tests such as Steer Clear are impaired in EDS, the correlation coefficient is not high.⁵⁶ On-road driving tests are not necessarily good instruments, since they tend to be of relatively short duration. On the other hand, equipping cars with on-board monitors is an expensive option. It has recently been reported that the use of a computer-based divided attention driving test (DADT) may be useful.⁵⁵ DADT represents a departure from standard vigilance testing in that it is long (multiple half-hour drives), boring, and uses several unfamiliar parameters. Briefly, it evaluates two major components of driving: tracking and visual search. The former is primarily responsible for keeping a vehicle on the road, while the latter is used to identify potential points of interest. The interface is similar to a steering wheel. However, graphics are kept simple to prevent excessive interest. George et al.⁵⁵ were able to demonstrate definite impairment in tracking errors in patients with EDS, as compared with controls, which were similar to that seen in control subjects pharmacologically impaired by alcohol. As in the case of vigilance testing, there was significant inter-subject variability in the results from DADT. Also, the MSLT only weakly correlated with driving results. Ideally, test results will eventually be correlated with automobile accident records.

QUALITY OF LIFE

Daytime symptoms, including sleepiness, irritability, depressed mood, and various aspects of cognitive dysfunction would be expected to impact patients' quality of life (QOL). However, individual measurements or a collective measurement of these symptoms would not be expected to adequately capture the most important aspects of SA patients' QOL that are a result of their breathing disorder. Measurement of QOL is now expected as an outcome measure in clinical trials. QOL indices can be generic, such as the Sickness Impact Profile (SIP),⁶⁶ the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),⁶⁷ or the Nottingham Health Profile (NHP).⁶⁸ These generic tests are useful

for comparing QOL across different disease states. Alternatively, QOL instruments can be developed for a specific disease state. For a QOL index to be useful in clinical trials, it should have the capacity to differentiate between people with a better QOL and those with a worse QOL (a discriminative index) and/or measure within-subject change following some method of intervention (an evaluative index).⁶⁹

To date, there has been little work completed on the measurement of QOL in people with SA. Gall et al.⁷⁰ used the SIP, the SF-36, and the psychosocial adjustment of illness scale to record QOL in 20 male patients diagnosed with mild SA (AHI < 20) and 22 male patients referred to their sleep lab who were found not to have SA following polysomnography. In comparison with the normal subjects, those with mild SA reported more sickness-related impairment in alertness, sleep, recreation, and work on the SIP. On the SF-36, SA patients reported lower social functioning, more limitations in function caused by physical and emotional reasons, and a lowered sense of well-being for mental health and energy than normal subjects. These patients also reported a poorer adjustment than normal subjects in their domestic, vocational, and social environments, including family relationships. In the randomized crossover trial of CPAP treatment for SA patients conducted by Engleman et al.,²² significant improvements in the NHP in 32 patients receiving CPAP were observed, compared with patients receiving placebo. Recently Finn et al.⁷¹ reported preliminary results on the use of the SF-36 in the Wisconsin Sleep Cohort Study of 740 subjects. Of the eight domains of the SF-36, five of them had a significant relationship to SA severity as judged by the AHI after controlling for age, body mass index, and gender. These five domains were role limitations caused by physical problems, social functioning, mental health, energy/fatigue, and general health perceptions.

The SIP measures health status by determining the degree of impact that sickness has had on a subject's life. It is organized into 12 categories (136 statements), 9 of which have statements that some SA patients would recognize were affected by sleep-disordered breathing. The NHP consists of 38 questions in a yes/no format that evaluate energy level, pain, emotional reactions, sleep, social isolation, and physical abilities. Of these questions, fewer than one half of them might be expected to be affected by SA. The SF-36 consists of eight multi-item scales that contain between two and ten items each. Questions focus on the limitations subjects have experienced as a result of their health (physical functioning), the impact on their work or other daily activities and on their social activities from physical health or emotional problems, and the degree to which their energy level (vitality) has been affected. There are also questions about general health, mental health, and bodily pain. Of the 36 questions, 13 involve aspects of a person's life that could be affected if they suffered from SA.

These generic QOL scales would be expected to capture some, but not all the important areas of QOL

for SA patients. Therefore, we have completed preliminary work on a disease-specific QOL index for SA patients that would be available for clinical trials to evaluate treatment outcomes. The Calgary SA Quality of Life Index (SAQLI)^{72, 73} was developed according to published guidelines that have been used previously to develop disease-specific instruments for disorders such as congestive heart failure,⁷⁴ COPD,⁷⁵ and asthma.⁷⁶ Initial interviews with small groups of patients, a review of the literature, opinions from several SA experts, and detailed one-on-one interviews with 40 SA patients highlighted major areas that were deemed important to SA patients' QOL. These areas included work or normal daily routine, family relationships, social interactions, driving safety, emotions/moods, exercise and leisure, health and self-perception, over 20 symptoms, and treatment-related symptoms. A relatively long, 133-item questionnaire was generated and presented to over 100 SA patients. For each item they were asked the following: (1) if it was or had been a problem; (2) if yes to 1, how important had it been to their QOL; and (3) if they had received treatment for SA, how much had this problem improved. The results from these interviews revealed that some of the more important QOL issues to SA patients relate to the fact that they often have to force themselves to accomplish their normal daily routine or they have an inability to get home maintenance chores accomplished because of a lack of energy. There also was a definite tendency for patients to want to do less socializing and to experience difficulty being able to read. Patients also expressed concern and stress over how bothersome their snoring was to their bed partner. There were definite emotional and mood factors attributed to SA such as irritability, depression, and frustration. The results were used to reduce the number of items, which were then organized into four domains: role functioning, social interactions, emotional functioning, and symptoms. The Calgary SAQLI is currently undergoing testing to document its reliability as well as its validity and responsiveness as an evaluative instrument. We believe it will be better able to capture the aspects of QOL that are important to SA patients and that have potential for improvement with treatment than generic QOL measures. It is unique in that it includes a domain of treatment-related symptoms to capture the potentially negative consequences of treatment on patients' QOL, which may provide a more realistic reflection of the net effect of treatment.

CONCLUSIONS

Sleep-disordered breathing is a common condition, afflicting between 2% and 4% of the adult population. These individuals experience symptoms of excessive daytime sleepiness to varying degrees, as well as other significant symptoms that have an adverse impact on their lives. There is an association between SA and depressive symptoms, cognitive functioning, alertness, and performance. However, traditional measures of SA severity do not correlate well with current measures of

alertness, performance, QOL, or even sleepiness, which serves to highlight our lack of understanding of these complex interactions. Regarding QOL, there is a striking lack of information available to help guide decisions such as treatment, or that compares QOL in patients with SA to those suffering from other chronic debilitating conditions. Further investigation in areas of cognitive functioning, performance, and QOL is needed for patients with sleep-disordered breathing.

Development of the Calgary SAQLI was made possible through grants from the Alberta Lung Association.

REFERENCES

- Burwell CS, Robin ED, Whaley RD, et al. Extreme obesity associated with alveolar hypoventilation: a pickwickian syndrome. *Am J Med* 1957;59:343-7.
- Lugaresi E, Cirignotta F, Montagna P, Sforza E. Snoring: Pathogenic, clinical and therapeutic aspects. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. Philadelphia: W.B. Saunders, 1994:621-9.
- Phillipson EA. Sleep apnea: a major public health problem. *N Engl J Med* 1993;328:1271-2.
- Guilleminault C, Dement WC. Sleep apnea and related sleep disorders. In: Williams RL, Koracon I, eds. *Sleep disorders: diagnosis and treatment*. New York: John Wiley, 1978:9-28.
- Bradley TD, Phillipson EA. Central sleep apnea. *Clin Chest Med* 1992;13:493-505.
- Strohl KP, Cherniack NS, Gothe B. Physiological basis of therapy for sleep apnea. *Am Rev Respir Dis* 1986;134:791-802.
- Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med* 1976;27:465-84.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1994;328:1230-5.
- Douglas NJ, Pollo O. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet* 1994;344:653-5.
- Shepard JW. Gas exchange and hemodynamics during sleep. *Med Clin North Am* 1985;69:1243-65.
- Ringler J, Basner RC, Shannon R, et al. Hypoxemia alone does not explain blood pressure elevations after obstruction apneas. *J Appl Physiol* 1990;69:2143-8.
- Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. *Arch Intern Med* 1992;152:538-41.
- Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd MS, Suratt PM. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. *Chest* 1986;90:686-90.
- Berry DTR, Webb WB, Block AJ, Bauer RM, Switzer DA. Nocturnal hypoxia and neuropsychological variables. *J Clin Neuropsychol* 1986;8:229-38.
- Flemons WW, Whitelaw WA, Brant R, Remmers JE. Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med* 1994;150:1279-85.
- Strohl KP, Redline S. Recognition of obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;154:279-89.
- Guilleminault C, Stoohs R, Clerk A, Simmons J, Labanowski M. From obstructive sleep apnea syndrome to upper airway resistance syndrome: consistency of daytime sleepiness. *Sleep* 1992;15:513-6.
- Guilleminault C. Clinical features and evaluation of obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. Philadelphia: W.B. Saunders, 1994: 667-77.
- Hudgel DW. Neuropsychiatric manifestations of obstructive sleep apnea: a review. *Int J Psychiatry Med* 1989;19:11-22.
- Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. *Lancet* 1981;1:862-5.
- Pollo O, Berthon-Jones M, Douglas NJ, Sullivan CE. Management of obstructive sleep apnoea/hypopnoea syndrome. *Lancet* 1994;344: 655-60.
- Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994;343:572-5.
- Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996;109:1269-75.
- Larsson LH, Carlsson-Nordlander B, Svanborg E. Four-year follow up after uvulopalatopharyngoplasty in 50 unselected patients with obstructive sleep apnea syndrome. *Laryngoscope* 1994;104:1362-8.
- American Thoracic Society. Sleep apnea, sleepiness, and driving risk. *Am J Respir Crit Care Med* 1996;150:1463-73.
- Bixler ED, Kales JD, Scharf MB, et al. Incidence of sleep disorders in medical practice: a physician survey. *Sleep Res* 1976;5:160.
- Broughton R, Ghanem Q, Hishikawa Y, Sugita Y, Nevssimalova S, Roth B. Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. *Can J Neurol Sci* 1981;8:299-304.
- George CFP, Nickerson P, Hanly P, Millar T, Kryger M. Sleep apnea patients have more automobile accidents. *Lancet* 1987;1:477.
- Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. *Am Rev Respir Dis* 1988;138:337-40.
- Mitler M, Carskadon M, Czeisler C, Dement W, Dinges D, Graeber R. Catastrophes, sleep, and public policy: consensus report. *Sleep* 1988;11:100-9.
- Hoddes E, Zarcone V, Smythe H, et al. Quantification of sleepiness: a new approach. *Psychophysiology* 1973;10:431-6.
- Johns MW. A new method of measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540-5.
- Hardinge FM, Pitson DJ, Stradling JR. Use of the Epworth sleepiness scale to demonstrate response to treatment with nasal continuous positive airway pressure in patients with obstructive sleep apnea. *Respir Med* 1995;89:617-20.
- Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea: the Epworth Sleepiness Scale. *Chest* 1993;103:30-6.
- Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness. *Sleep* 1986;9:519-24.
- Carskadon MA, Dement WC. Effects of total sleep loss on sleep tendency. *Percept Mot Skills* 1979;48:495-506.
- Nicholson AN, Stone BM. Impaired performance and the tendency to sleep. *Eur J Clin Pharmacol* 1986;30:27-32.
- Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr Clin Neurophysiol* 1978;45:621-7.
- Kribbs NB, Pack AI, Kline LR, Dinges DF, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;146:1162-8.
- Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 1982;52:658-61.
- Sangal RB, Thomas L, Mitler MM. Maintenance of wakefulness test and multiple sleep latency test: measurement of different abilities in patients with sleep disorders. *Chest* 1992;101:898-902.
- Kales A, Caldwell AB, Cadieux RJ, Vela-Bueno A, Ruch LG, Mayes SD. Severe obstructive sleep apnea—II: Associated psychopathology and psychosocial consequences. *J Chron Dis* 1985;38:427-34.
- Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of obstructive sleep apnea: a review. *J Clin Psychiatry* 1989;50:348-51.
- Derderian SS, Bridenbaugh RH, Rajagopal KR. Neuropsychologic symptoms in obstructive sleep apnea improve after treatment with nasal continuous positive airway pressure. *Chest* 1988;94:1023-7.
- Reynolds CF, Kupfer DJ, McEachran AB, Taska LS, Sewitch DE, Coble PA. Depressive psychopathology in male sleep apneics. *J Clin Psychiatry* 1984;45:287-90.
- Cassel W. Cognitive effects and daytime sleepiness: psychosocial

- sequelae of sleep disordered breathing. Sleep apnea and personality. Sleep 1993;16:S56-8.
47. Lee S. Depression in sleep apnea: a different view. J Clin Psychiatry 1990;51:309-10.
 48. McDowell I, Newell C. Measuring health: a guide to rating scales and questionnaires. New York: Oxford University Press, 1987:139-51.
 49. Bearpark H, Grunstein R, Touyz S, Channon L, Sullivan C. Cognitive and psychological dysfunction in sleep apnea before and after treatment with CPAP. Sleep Res 1987;16:303.
 50. Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. Sleep 1987;10:254-62.
 51. Telakivi T, Kajaste S, Partinen M, Koskenvuo M, Salmi T, Kaprio J. Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep related hypoxic events. Sleep 1988;11:454-62.
 52. Yesavage J, Bliwise D, Guilleminault C, Carskadon M, Dement W. Preliminary communication: intellectual deficit and sleep-related respiratory disturbance in the elderly. Sleep 1985;8:30-3.
 53. Klonoff H, Fleetham J, Taylor DR, Clark C. Treatment outcome of obstructive sleep apnea: physiological and neuropsychological concomitants. J Nerv Ment Dis 1987;175:208-12.
 54. Flemons WW, Remmers JE, Whitelaw WA. The correlation of a computer simulated driving program with polysomnographic indices and neuropsychological tests in consecutively referred patients for assessment of sleep apnea. Sleep 1993;16(suppl 8):S71.
 55. George CFP, Boudreau AC, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1996;154:175-81.
 56. Findley L, Unverzagt M, Suratt P, et al. Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. Chest 1995;108:619-24.
 57. Wilkinson RT. Effects of up to 60 hours' sleep deprivation on different types of work. Ergonomics 1964;7:175-86.
 58. Horne JA, Pettitt AN. High incentive effects on vigilance performance during 72 hours of total sleep deprivation. Acta Psychol 1985;58:123-39.
 59. Donnell JM. Performance decrement as a function of total sleep loss and task duration. Percept Mot Skills 1969;29:711-4.
 60. Monk TH. Circadian rhythms in subjective activation, mood, and performance efficiency. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: W.B. Saunders, 1994:321-30.
 61. Light AI, Sun JH, McCool C, Thompson L, Heaton S, Bartle EJ. The effects of acute sleep deprivation on level of resident training. Curr Surg 1989;46:29-30.
 62. Wilkinson RT, Houghton D. Field test arousal: a portable reaction timer with data storage. Hum Factors 1982;24:487-93.
 63. Dinges DF, Orne MT, Whitehouse WG, Orne EC. Temporal placement of a nap for alertness: contributions of circadian phase and prior wakefulness. Sleep 1987;10:313-29.
 64. Findley L, Fabrizio M, Knight H, et al. Driving simulator performance in patients with sleep apnea. Am Rev Respir Dis 1989;140:529-30.
 65. Colquhan WP. Circadian variations in mental efficiency. In: Colquhan WP, ed. Biological rhythms in human performance. London: Academic Press Inc, 1971:39-108.
 66. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.
 67. Ware J, Sherbourne C. The MOS 36-item short-form health survey 1: conceptual framework and item selection. Med Care 1992;30:473-81.
 68. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E. The Nottingham Health Profile: subjective health status and medical consultations. Soc Sci Med 1981;15A:221-9.
 69. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118:622-9.
 70. Gall R, Isaac L, Kryger M. Quality of life in mild obstructive sleep apnea. Sleep 1993;16:S59-61.
 71. Finn L, Young T, Palta M, Evans L, Dempsey J, Fryback D. Association of unrecognized sleep disordered breathing and general health status in the Wisconsin sleep cohort study [Abstract]. Am J Respir Crit Care Med 1996;153:A358.
 72. Flemons WW, Ontonio LR, Reimer M. The development of a sleep apnea quality of life index [Abstract]. Am J Respir Crit Care Med 1996;151:A748.
 73. Flemons WW, Reimer M. The Calgary sleep apnea quality of life index [Abstract]. Am J Respir Crit Care Med 1996;153:A353.
 74. Guyatt GH, Norgradi S, Halcrow S, Singer J, Sullivan MJJ, Fallen EL. Development and testing of a new measure of health status for clinical trials in heart failure. J Gen Intern Med 1989;4:101-7.
 75. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773-8.
 76. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147:932-8.