Review Article

Consequences of obstructive sleep apnoea

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A plethora of medical consequences have been associated with the syndrome of obstructive sleep apnoea (OSA). These are global, affecting nearly every body function, and have been related to two key pathophysiological findings in sleep apnoea: repetitive falls in oxyhaemoglobin saturation during sleep, and recurrent arousals from sleep which terminate apnoea episodes. Sufferers of OSA may experience daytime sleepiness, which has been measured both subjectively using the Epworth Sleepiness Scale and the Stanford Sleepiness Scale, but also objectively, using Multiple Sleep Latency Testing, Maintenance of Wakefulness testing, and the Oxford Sleep Resistance test. In addition to the loss of alertness, sleep apnoea contributes to memory deficits, reduced vigilance, impaired executive function, increased risk for automobile and occupational accidents, and decreased quality of life. Importantly, afflicted individuals experience improvements in these outcomes with treatment. Taken together, this evidence forms a compelling basis to identify and treat latent cases of sleep apnoea. Not only do patients have the opportunity to achieve improvements in these outcomes and health-related quality of life, but the enormous economic burden that untreated apnoea imposes on the health care system may be eased.

Key words Day time sleepiness - health care cost - obstructive sleep apnoea - quality of life - traffic accidents - vigilence

Introduction

Obstructive sleep apnoea (OSA) has been associated with a host of medical consequences that affect virtually every major organ system. A constellation of symptoms has been described, which include snoring, daytime sleepiness, restless sleep, nocturnal enuresis, irritability, depression, memory deficits, inability to concentrate, and decreased alertness. Other outcomes include increased errors, reduced vigilance, impaired work efficiency, increased risk for automobile and occupational accidents, and decreased quality of life. Postulated mechanisms have included hypoxaemia and sleep fragmentation, and treatment has been shown to reduce sleepiness while improving mood disturbances, cognition, and performance. This review provides information on some of the major health consequences of OSA, with special emphasis on its effects on sleepiness, cognition, driving, quality of life and economic costs. A review of cardiovascular consequences is included elsewhere in this issue1.

Sleepiness

Although fatigue, tiredness and lack of energy may be even more common complaints of sleep apnoea sufferers than daytime sleepiness2, sleepiness still
remains one of the best characterized symptomatic consequences of OSA. The assessment of sleepiness has included subjective scales, such as the Epworth Sleepiness Scale, which is commonly used in clinical settings and asks patients to rate the likelihood of falling asleep in eight different sedentary situations on a Likert scale. Another tool, the Stanford Sleepiness Scale, has been used to quantify the degree of subjective sleepiness, and its use has largely been confined to research settings.

Subjective assessments of sleepiness are not always reliable or appropriate, as for example, in pre-employment screening to determine fitness eligibility in industries such as commercial driving and commercial aviation. In such arenas, under-reporting of symptoms among patients may be driven by economic pressures.

Alternative measures are available to quantify sleepiness, which rely on objective determinations performed in the laboratory setting. The most commonly used objective tool to assess sleepiness in the clinical setting is the Multiple Sleep Latency Test (MSLT), which measures the tendency of the patient to fall asleep in a series of nap opportunities. Another tool, the Maintenance of Wakefulness Test (MWT), measures the patient’s volitional ability to stay awake, and has gained popularity in pre-employment evaluations. The MWT offers four 40-minute challenges to remain awake during the day in quiet, non-stimulating conditions. A review of both has been conducted recently. Another tool that has emerged is the Oxford Sleep Resistance (or OSleR) test. Like the MWT, the OSleR also consists of a series of four 40-min opportunities to resist sleep in a sedentary environment. While the MWT relies on EEG determination of sleep onset, the OSleR is a behavioural test which requires the participant to demonstrate wakefulness by responding to a light stimulus by pressing a button.

The correlation between subjective and objective measures of sleepiness, however, remains weak to moderate. Interestingly, even objective assessments of sleepiness using the MSLT or MWT correlate only moderately well with the severity of apnoea. Other limitations of these tests include the paucity of normative data, as well as their limited applicability in situations such as night shift work and at the extremes of ages.

Kapur et al. reported the cross-sectional prevalence of subjective sleepiness in patients with moderate to severe sleep apnoea using retrospective data from the community-based, Sleep Heart Health cohort of 6,440 subjects. Participants who often complained of excessive sleepiness or feeling unrefreshed, or who had an Epworth score > 10 were identified as sleepy. Forty-six per cent of subjects with moderate to severe sleep-disordered breathing (n = 1149) reported sleepiness. Importantly, then, most people with sleep-disordered breathing did not report experiencing any sleepiness. Four coexisting medical conditions appeared to be associated with sleepiness: partial sleep deprivation, obstructive lung disease, insomnia, and awakenings due to nocturnal leg cramps and movement. Interpretation of these data, however, is limited by potential residual confounding.

Polysomnographic measures of sleep stage percentages and sleep disruption have not been consistently associated with sleepiness – perhaps because of their tendency to record a single night’s recording of sleep, which is subject to night-to-night variability.

Cognitive deficits

In the individual who suffers from untreated sleep apnoea, deficits may occur in a variety of brain functions, due both to sleep loss (in the form of sleep fragmentation or lack of slow wave sleep) or recurrent hypoxaemia. Deficits in memory and in short and sustained attention have been ascribed to sleepiness, while deficits in verbal functioning, problem-solving and executive functions have been attributed to hypoxaemia.

These deficits appear to intensify with increasing OSA severity. In a prospective evaluation, increasing severity of nocturnal breathing disturbance, and extent of sleep disruption were identified as determinants of cognitive impairment, in addition to the magnitude of hypoxaemia. Impairment in several executive brain functions has been described, including difficulty in initiating new mental processes and to inhibit automatic ones were present, perseverative errors, deficits of verbal and visual learning abilities, as well as reduced memory.

A standard battery of neuropsychological tests for apnoea patients has been proposed to allay differences in findings from one study to another that are related to the choice of test. For example, while self-reports may not confirm a correlation between sleep apnoea and decline in memory, such decline has been endorsed during objective testing. Cognitive deficits have been structurally associated with loss of gray
matter concentration within the left hippocampus and surrounding brain areas, and to more extensive loss of gray matter bilaterally in the parahippocampus. Basal slowing in information processing related to sleepiness has been proposed to explain many of the neurocognitive effects of sleep apnoea, and this conjecture has been supported by findings on functional MRI studies.

A key cognitive function that has been demonstrated to show decline in persons with sleep apnoea is vigilance. Vigilance has been proposed to be tested via a number of in-laboratory techniques, including the psychomotor vigilance test (PVT), the OSLeR test, and many others.

Of these available strategies, the PVT has emerged as extremely sensitive to sleepiness and as being practical and easy to use, without evidence of learning over repeat administrations, and has proved to be robust measure of vigilance in a wide range of conditions that cause sleepiness. The PVT measures reaction time in high signal-load conditions. Consequences of sleepiness demonstrated by the test include a slowing of responses, an increased propensity to lapse for lengthy periods, increased numbers of errors of commission, an enhanced time-on-task effect within a given test experience, and sensitivity to circadian and homeostatic sleep drives. A cross-sectional analysis of data from 265 female and 346 male middle- and older-aged adults enrolled in the Wisconsin Sleep Cohort Study showed that number of lapses and the number of false responses in the PVT correlated with the apnoea-hypopnoea index (AHI), independent of gender and obesity among participants > 65 yr in age.

In elderly subjects, the question of whether decline in cognition has also been assessed by the mini-mental status examination (MMSE), a question of whether a decline in MMSE score may be mediated by the presence of daytime sleepiness due to sleep apnoea has been addressed. In a community-dwelling group of elders over 65 in age with sleep apnoea, linear regression modeling showed an association between daytime sleepiness and declining cognitive function during a follow up period of 15 yr. Sleepiness was measured subjectively, however, and this correlation between cognitive decline and respiratory disturbance index was eliminated after the model was adjusted for other sleep-related variables. These include total sleep time, wakefulness after sleep onset, number of awakenings, arousal index, average oxyhaemoglobin saturation during sleep, and the presence of daytime sleepiness, snoring, and loud snoring.

Driving

One of the most ominous consequences of untreated OSA is automobile accidents, a topic that has been reviewed previously. In self reports, nearly 56 per cent of the general public admit to driving while drowsy, 22.6 per cent have fallen asleep while driving, and 4.7 per cent report crashing a vehicle because of sleepiness.

Cumulative data accrued over the past 20 yr in a series of studies indicate that the risk of a vehicular crash in a patient with untreated sleep apnoea ranges from 2 to 7-fold higher than a driver without apnoea, and that treatment of apnoea reduces crashes, related deaths and costs. Prior studies, however, have been limited in a number of ways: they have used self-reported crash information, rather than objective sources such as police records or insurance information; some have had small cohorts; some lacked a control group; some had patients with minor degrees of apnoea; some failed to account for potential confounding variables, including prior sleep duration, driving experience, engagement in night-shift work, driving exposure, BMI, use of sedating medications, and the presence of other sleep disorders.

Nevertheless, data from 40 studies on this topic have been reviewed recently, and support several findings that non commercial drivers with sleep apnoea experience a statistically significantly increased risk of involvement in motor vehicle crashes; that daytime sleepiness and the severity of sleep apnoea were not correlated consistently with crash risk; and that treatment of sleep apnoea improves driver performance.

The association between sleep apnoea and crashes was shown 20 yr ago by Findley et al., who compared the driving records of patients with OSA with those of 35 drivers without OSA. They reported a 7-fold greater rate of vehicular accidents among 29 patients with sleep apnoea compared to 35 drivers without apnoea. Subsequently, in 1989, a larger study was conducted by Aldrich et al. They compared data from 70 control subjects with that from 424 adults with any of four different sleep disorders: sleep apnoea, narcolepsy, other disorders of excessive sleepiness, and sleep disorders without excessive sleepiness. Sleepy drivers suffered sleep-related accidents at 1.5-4 times greater rates than did control subjects. In 1999, a carefully-conducted case-control study was done in Spain by Teran-Santos et al. Case patients consisted of 102 drivers
who received emergency hospital treatment after experiencing highway traffic accidents between April and December 1995. Within two months of the accident, they underwent sleep testing to confirm sleep apnoea. These drivers were compared to 152 patients randomly selected from primary care centers and matched with the case patients for age and sex. They found a strong association between the severity of sleep apnoea as estimated by the AHI, and the risk of traffic accidents. The study included predominantly middle-aged men: the average age was 44 yr, and 77 per cent were men. Those with an AHI ≥ 10 events/h on an overnight sleep study had an odds ratio of 6.3 (95% confidence interval, 2.4 to 16.2) for having a traffic accident. This relation persisted even after accounting for alcohol consumption, visual disturbances, body-mass index, driving experience, age, prior record of having traffic accidents, use of medications that cause drowsiness, and sleep schedule.

In the same year, George et al\textsuperscript{26} conducted a retrospective analysis that reviewed crash data compiled by the Ministry of Transportation of Ontario (MTO). They assessed accidents in the five years preceding the diagnosis of sleep apnoea. They compared these records against drivers in the MTO registry who did not have accidents, and were matched for age and gender. They ascribed risk of having a traffic accident to those with sleep apnoea who had severe disease, characterized by AHI >40 events/h. Driving exposure, however, was not controlled as rigorously in this study.

Whether this accident risk can be reduced by treatment of OSA with continuous positive airway pressure (CPAP) therapy was addressed in a publication that appeared one year later, which also controlled for driving exposure in the form of kilometers driven. Horstmann et al\textsuperscript{27} issued a questionnaire to 156 patients with sleep apnoea syndrome (SAS) and in 160 age-gender matched controls. They found that patients with moderate to severe SAS have an up to 15-fold risk increase of motor vehicle accidents: 12.4 per cent of those with OSA had motor vehicle accidents, compared against 2.9 per cent in the control group ($P<0.005$). Importantly, treatment with nasal CPAP nCPAP in 85 SAS patients resulted in reduction of the motor vehicle accident rate from 10.6 to 2.7 per million km ($P<0.05$). This finding has been supported in later studies\textsuperscript{28}, and the importance of diagnosing sleep apnoea and delivering effective treatment even in non-sleepy drivers has been emphasized.

Further support to diagnose apnoea and institute treatment among drivers comes from the nature of sleepiness-related crashes: whether these crashes simply cause minor property damage, or whether they result in injury or death. In 2008, Mulgrew et al\textsuperscript{29} reviewed not only the risk of crashes, but their severity as well. They reviewed provincial insurance records in Canada to determine the nature and type of crash for the three years preceding sleep studies among 783 patients with OSA. They compared these data with data for 783 age- and sex-matched controls. Patients with OSA had a 3.0-4.8-fold increased rate of a crash causing an injury, while those without apnoea (AHI 0–5 events/h) had crash rates similar to controls. They found a dose-response relationship: an increased rate of crashes that cause injuries as the severity of apnoea increased. Compared with patients with an AHI of 0–5 events/h, the relative risk of crashes that cause injury in patients with severe OSA (AHI >30/h) was 6.1 (95% CI 1.6 to 18.1). Patients with mild OSA (AHI 5–15 events/h) had a 4.9- fold (95% CI 1.5 to 16.1) increased risk of crashes involving personal injury compared with those with an AHI of 0–5 events/h.

Recently, our group\textsuperscript{30} ascertained the important role of short sleep duration in impaired performance in commercial truck drivers licensed in Philadelphia. Pack et al\textsuperscript{30} conducted full, in-laboratory sleep studies in 247 of 551 drivers at higher risk for apnoea and in 159 of 778 drivers at lower risk. The effects of severe apnoea, which occurred in 4.7 per cent, and of sleep duration less than 5 hours/night, which occurred in 13.5 per cent, were similar in terms of their impact on objective sleepiness. Thus, addressing impairment in commercial drivers requires addressing both insufficient sleep and sleep apnoea, with short sleep duration being more common problem.

Given the high prevalence of sleep apnoea in commercial drivers\textsuperscript{27-29}, and the risk of traffic accidents if apnoea is left untreated, our group also conducted a novel economic analysis to determine whether routine screening and treatment of OSA among commercial drivers can be justified\textsuperscript{31}. We compared the costs of three programmes: (i) in-lab polysomnography; (ii) selective in-lab polysomnography for high-risk drivers, where high risk is first identified by body mass index, age and gender, followed by oximetry in a subset of drivers; and (iii) not screening. Among community-based holders of commercial driver's licenses, we summed the costs for each of these three programmes. These equaled the sum of the costs of testing, treatment of identified cases, and crashes. Assuming that treatment prevents apnoea-related crashes, we
found that in-laboratory polysomnography is not cost-effective as a mass screening tool, because it was more expensive than the cost of crashes when no screening is done. We found that strategies that reduce reliance on in-laboratory polysomnography (such as oximetry) may be more cost-effective than not screening, and that treatment acceptance may need to be a condition of employment for affected drivers, so that crash risk may be adequately reduced and the cost of screening economically justified.

Given these compelling data that correlate crash risk with the occurrence of apnoea, the reduction in risk with CPAP therapy, the high cost of sleepiness-related crashes in commercial drivers and their relationship to bodily injury and death, attempts have been made to predict risky drivers a priori using driving simulators. Although several of these have been developed and tested, no studies have shown that performance on these simulators correlates with actual on-the-road driving performance.

**Quality of life**

The severity of the sleep apnoea itself, the experience of daytime sleepiness, the alteration in sleep stages and sleep architecture, obesity, sleep fragmentation and hypoxaemia may alone or in combination cause the reduction in quality of life that has been observed in sleep apnoea patients. Quality of life has been assessed using mean score profiles on the SF-36 questionnaire in community-based adults enrolled in the Sleep Heart Health Study. These data indicate that OSA and its related sleep symptoms reduce health-related quality of life to a degree that is comparable with other chronic illnesses.

Data from the large, multi-center, cross-sectional and community-based Sleep Heart Health Study indicate that impaired quality of life in patients with sleep disordered breathing is related to difficulty initiating and maintaining sleep, to excessive daytime sleepiness, and to the severity of sleep disordered breathing. Mild to moderate sleep disordered breathing was associated with diminished vitality on the SF-36 scale, while severe sleep-disordered breathing was associated more globally with poorer quality of life. Subjective sleep symptoms were comprehensively associated with poorer quality of life on the SF-36 instrument.

In addition to general questionnaires such as the SF-36, two major indices, the Functional Outcomes of Sleep Questionnaire (FOSQ) and the Calgary Sleep Apnoea Quality of Life Index (SAQLI), have emerged to assess disease-specific quality of life in patients with sleep apnoea. Domains assessed by the FOSQ included activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. The SAQLI assesses daily functioning, social interactions, emotional functioning, and symptoms. Both scales show decrements in quality of life in patients with sleep apnoea. Importantly, encouraging data have emerged that quality of life improves in patients whose apnoea is treated effectively.

Patients with sleep apnoea experience a host of symptoms and derangements that may impact on quality of life, including nocturia, neuroendocrine dysfunction, abnormal secretion of atrial natriuretic factor, dysfunction of the pituitary-gonadal axis leading to diminished libido and erectile dysfunction in men, and reduced levels of female sex hormones in women. Sleepiness may mediate some of these effects among men with daytime sleepiness assessed by the Epworth Sleepiness Scale, 80 per cent had erectile dysfunction compared with 20 per cent of the men with normal Epworth Sleepiness Scale scores. The severity of sleep-disordered breathing may mediate other effects - the occurrence of more than three episodes of nocturia per night may indicate the presence of severe sleep-disordered breathing. In men, sleep apnoea has been shown to decrease plasma insulin-like growth factor-1 (IGF-I), testosterone and sex hormone binding globulin levels to a degree that is proportional to the degree of severity of and frequency of oxyhaemoglobin desaturation. These hormonal derangements, as well as the level of atrial natriuretic factor, improve with CPAP therapy and are independent of age and obesity.

**Economic consequences**

Reviewed previously, the data regarding economic consequences of untreated sleep apnoea are limited, but show a trend towards increased health care costs and increased utilization of health care services. Studies that have evaluated health care utilization during 10 yr, 2 yr and 1 yr before sleep apnoea is diagnosed, suggest that patients are heavy users of health care even before the diagnosis of sleep apnoea is made, and that patients with more severe apnoea use health care resources even more substantially.

The severity of sleep-disordered breathing was associated with increased medical costs. Untreated sleep apnoea may have caused $3.4 billion additional medical costs in the U.S. in 1999. A more extended
study evaluated health care utilization during the 10 yr prior to diagnosis among 181 patients, and compared them to randomly selected controls who were matched for age, gender and geographic location. Patients with sleep apnoea used twice as many health care services in the 10 yr prior to their initial diagnostic evaluation for apnoea.

A pertinent question that then arises is whether this gap in health care utilization narrows after sleep apnoea is diagnosed and treated. Bahammam et al addressed this question using a prospective observational design. Physician claims and hospital stays declined among patients who adhered to treatment. Whether the absolute amount of expenditure (rather than the difference) also declined, however, was not reported.

Of relevance to clinicians and economists remains the question of which patients with sleep apnoea are most likely to utilize health care more heavily. Age exceeding 65 yr and female gender were the strongest predictors of health care utilization, using measures such as emergency department visits, consultations, hospital admissions and medication use. In this study, all patients with sleep apnoea had equal access to health care, eliminating this as a potential confounding variable. Counter-intuitively, body mass index and classic sleep apnoea severity indices, such as respiratory disturbance index and arousal index, did not predict health care utilization.

Conclusion

OSA is associated with a host of health consequences. These include a wide range of symptoms, decrements in cognition, driving and quality of life, and results in increased health care utilization and health care costs. A cardinal symptom of OSA, daytime sleepiness, occurs in the setting of fragmented sleep architecture due to arousals related to recurrent apnoea terminations. Sleepiness may be measured subjectively, using tools such as the Epworth Sleepiness Scale, or objectively in the laboratory, using the Multiple Sleep Latency Test (MSLT). Decrements in cognitive function span multiple areas, such as vigilance, memory, concentration, and executive function. Sleepiness and reduced cognition may contribute to driving risk and fall-asleep crashes, which can contribute to huge costs, particularly in occupational settings such as commercial driving. Patients with sleep apnoea also experience subjectively reduced quality of life and functioning, measured by general scales such as the SF-36, as well as disease-specific indices such as the Functional Outcomes of Sleep Questionnaire and the Calgary Sleep Apnoea Quality of Life Index. Overall, this host of consequences translates to a huge economic burden on society, with apnoea patients consuming more health care resources for at least 10 yr prior to disease recognition.

Taken together, these data indicate an urgency to make the diagnosis promptly in suspected cases, and, importantly, to institute timely therapy. It is encouraging to note that many of the health consequences of sleep apnoea improve with effective therapy, including sleepiness, quality of life, cognition and driving risk, suggesting that increasing awareness of the problem among health care providers and improving access to sleep health services should be important first steps in improving the overall well-being of affected patients.

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References


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