

Psychologic Aspects of Obstructive Sleep Apnea/Hypopnea Syndrome

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Abstract

A wide range of psychologic symptoms are correlated with sleep apnea/hypopnea syndrome (SAHS). The question of whether these may be comorbidities, causes, or consequences, and the possible mechanisms involved, are examined through a review of relevant studies. The recent recognition of fatigue as an important, but relatively unrecognized, symptom in sleep apnea is highlighted. The authors propose that fatigue in SAHS may function as a possible mediator for a range of psychologic and behavioural impairments.

Keywords

Obstructive sleep apnea/hypopnea syndrome (SAHS), depression, anxiety, post-traumatic stress disorder (PTSD), sleepiness, fatigue

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Obstructive sleep apnea/hypopnea syndrome (SAHS) is characterized by numerous episodes of airway collapse during sleep, leading to significant reduction or complete blocking of air flow. As a result, the individual experiences repeated arousals and recurrent drops in arterial oxygen saturation. SAHS severity is commonly gauged using the Respiratory Disturbance Index (RDI: number of respiratory disturbances per hour of sleep) and measures of oxyhemoglobin saturation (SpO₂).¹ It has been estimated to affect 5 % of adults,² although its prevalence may be increasing because of recent obesity trends.³

Relationship Between Sleep Apnea/Hypopnea Syndrome and Psychologic Factors

The relationship between SAHS and psychologic symptoms has been investigated for decades. In particular, a link between SAHS and comorbid depression and depressive symptoms has been demonstrated in many early studies to 1997.⁴ Depressive symptoms have been variously termed depression, mood disturbance or disorder and dysphoric mood; this appears to be related to the terminology in the specific measures used. Some of the studies reviewed include individuals with a diagnosis of depression; others evaluate variation in depressive symptoms, both as states and traits that do not fall into the pathological range. For the purposes of this article, the various terms are all considered to be in the category of depressive symptoms.

Recent epidemiologic evidence has corroborated the early findings on the comorbidity of depression in individuals with SAHS.^{5,6} Multiple studies have suggested that sleep apnoea severity is associated with mood disorders.⁷⁻⁹ Other studies, however, have reported no clinically significant levels of depressive symptoms in individuals with SAHS.¹⁰⁻¹⁴

As is true of the population at large, women appear to have more depressive symptoms than men, even when there is no sex difference in apnoea severity.¹⁵ Some studies have found links between SAHS and psychologic disorders such as anxiety and post-traumatic stress disorder,⁵ while others have failed to find such relationships.^{16,17} Cognitive deficits were found to be associated with frequency of apneas/hypopneas, arousals and hypoxemia.¹⁶

Several studies have shown that quality of life in patients with SAHS is impaired compared with normal samples.^{11,18,19} Many of these studies used the short-form health questionnaire SF-36,²⁰ which quantifies self-perceptions concerning general health and functional wellbeing. Mild to moderate sleep-disordered breathing was found to be associated with a lower score on the Vitality scale of this measure, while severe sleep-disordered breathing was more broadly associated with a number of scales making up this quality-of-life measure.²¹

Correlates, Causes and Consequences

Clearly, a wide range of psychologic symptoms are correlated with SAHS. The questions arise: Are these simply comorbidities? Are there causal aspects to be discovered? Might some psychologic symptoms be consequences of the disease?

A suggestive study examined the association of psychosocial job stress with sleep-related breathing disturbance in a cross-sectional sample of 1,940 men working in small and medium-sized enterprises in Japan.²² Interestingly, it was found that workers exposed to such variables as a low levels of social support from supervisors, high levels of job-future ambiguity, interpersonal conflict at the workplace and variance in

workload had significantly higher prevalence of sleep-related breathing disturbance compared with counterparts with lower exposure to these situational stressors. Furthermore, the association strengthened as job stress increased. Interpretation of these findings is severely limited, however, because of the cross-sectional nature of the design and, more importantly, the fact that sleep-related breathing disorder was measured by a single question: Have you ever felt difficulty breathing during sleep or has anyone in your family told you that you have such difficulty?

The association between post-traumatic stress and sleep apnea has been investigated primarily by Krakow and his associates.²³⁻²⁷ The research is intriguing, but inconclusive due to methodologic problems.²⁸ According to Krakow, a high percentage of people with diagnosed post-traumatic stress disorder (PTSD) also have sleep-related breathing disorders, including obstructive sleep apnea and upper airway resistance syndrome. Prevalence estimates appear difficult to establish, in part because in some studies only a small percentage of the sample was evaluated with polysomnography (PSG) in the sleep laboratory.

However, of those who were evaluated in a sleep laboratory, approximately 90 % of individuals with PTSD were found to have a sleep-related breathing disorder.²³ In a study in which PTSD patients with diagnosed sleep-related breathing disorders were compared with a matched sample (age and sex) of sleep clinic patients, Krakow et al.²³ evaluated the characteristics of their self-reported sleep as well as their objective diagnoses. The PTSD group was characterized by more frequent diagnosis of upper airway resistance syndrome, and less of obstructive sleep apnea. Those with PTSD also had more frequent diagnosis of periodic limb movement disorder, more frequent self-reported sleep disturbance and greater cognitive/ affective distress than the sleep clinic sample. Both groups reported similar frequencies of daytime sleepiness and fatigue, morning headache, dry mouth and nocturia—all common symptoms of sleep apnea.

Recently, there is increasing evidence that implicates disruption of the hypothalamic–pituitary–adrenal (HPA) axis in post-traumatic stress disorder.²⁸⁻³¹ The HPA axis is the neuroendocrine system responsible for modulating the stress response in humans. It helps regulate sleep as well.³¹ In addition, there is growing evidence that deregulation of the HPA axis during stress is associated with the onset of major depression in predisposed individuals.³²

Individuals with chronic fatigue syndrome (CFS) comprise another clinical group that has demonstrated a high frequency of sleep disorders. For example, among the diagnostic criteria for CFS is sleep disturbance, including the complaint of non-refreshing sleep.^{33,34} In addition, our own studies^{35,36} have identified a very high frequency of diagnosed SAHS in a sample of volunteers with CFS, a finding that has been substantiated by others.^{37,38} CFS is currently seen as a condition of unknown etiology, characterized by abnormalities in immune, endocrine and neurologic function. Several studies have noted associated impairment of HPA axis function in this population as measured by plasma cortisol levels.^{39,40}

Recent reviews have pointed to evidence that SAHS causes impairment of HPA axis function through sleep disruption and hypoxemia; long-term

continuous positive airway pressure (CPAP) therapy may restore normal plasma cortisol profiles.⁴¹⁻⁴³ These studies point to the possibility that environmental stress, or the physiological stress response itself, may play an active role in the development of SAHS. The interrelationships between stress mechanisms and SAHS are complex and poorly understood at present. Nevertheless, these have important research and practical implications for the future.

Such findings also point to the importance of examining the relationship path in other conditions associated with SAHS. For example, one study set out to examine whether depressive symptoms are independently associated with poorer self-reported sleep quality after controlling for polysomnographic measures of sleep. The results indicate that self-reported sleep quality (as measured by the Insomnia Severity Index)⁴⁴ among individuals with relatively severe SAHS was not related to polysomnographic measures of sleep quality; nor was self-reported sleep quality related to the RDI or to the body mass index (BMI). However, it was strongly related to depressive symptoms.⁴⁵

Such results raise questions about whether elevated depression scores in patients with SAHS precede or coincide with SAHS symptoms. Are depressive symptoms just an epiphenomenon of the SAHS condition? For example, somatic symptoms such as feelings of fatigue, lack of energy and irritability are widely regarded as typical clinical sequelae of SAHS.⁴⁶ Such symptoms are also hallmarks of depression.⁷ Are the symptoms, then, related to a distinct psychiatric disorder, or do they more accurately reflect the consequences of sleep apnea? One possible explanation of the conundrum is that the relationship between SAHS and depression is indirect – that it is mediated by correlates of SAHS, such as obesity.

Mediating Factors

Several variables have been examined as potential mediators in the association between SAHS and depression. These include physiological factors such as obesity, hypertension, cardiovascular disease, chronic heart failure, diabetes, oxygen desaturation and age as well as psychological factors such as quality of life, daytime sleepiness, daytime fatigue and sleep disruption.

Obesity is the strongest risk factor for the development of SAHS.^{47,48} There is increased depression among obese subjects, although SAHS may have been an important unmeasured confounding variable.^{49,50} Aloia and his colleagues⁷ designed a study to determine the degree to which apnea severity and obesity independently contribute to the relationship between depressive symptoms and SAHS. They were also interested in examining the degree to which these relationships are moderated by gender. Participants were recruited as part of a large-scale study investigating the effects of continuous positive airway pressure (CPAP) treatment adherence on psychological functioning. One-third of their sample scored in the mild to severe range for depression, as measured by the Beck Depression Inventory (BDI)-II.⁵¹ This measure permits separate evaluation of the cognitive and somatic dimensions of depression. The results indicate that participants with greater apnoea severity tended to be both more obese and more depressed. However, the investigators found that apnoea severity was only related to the somatic dimension of depression, while obesity

was related to the cognitive aspect. Gender appeared to moderate the relationships between apnoea severity, obesity and depression. Men only showed a relationship between apnoea severity and somatic complaints associated with depression, independent of obesity. Women only showed a relationship between obesity and the cognitive aspect of depression, independent of apnoea severity. This study highlights the complex nature of the construct of depression as it relates to SAHS.

SAHS also has been found to be independently associated with an increased risk of hypertension, cardiovascular disease and chronic heart failure.^{52,53} To address an aspect of the complexity of the relationship, another team of investigators examined psychological and sleep variables in a sample of individuals with and without sleep apnea, some of whom were normotensive and some hypertensive.⁴ They found several patterns of relationships between sleep and psychological measures, and the patterns differed for individuals with SAHS and those without. For participants with SAHS, general mood disturbance was primarily associated with amount of rapid eye movement (REM) sleep. Depression was positively related to deep sleep, and anger was positively related to hypoxaemia. When age, body weight and hypertension were controlled for statistically, for patients with SAHS the variable 'vigour' (measured by the Profile of Mood States [POMS]⁵⁴) was correlated with total sleep time, but many of the relationships between sleep and mood disappeared. The findings suggested that depression and total mood disturbance were related more to age, weight and/or hypertension than they were to SAHS. The investigators concluded that many of the previously reported links between mood and sleep in individuals with sleep apnoea disappear after controlling for covariates such as age, weight and hypertension and for individuals without SAHS, there are fewer relationships between dysphoric mood and sleep.

Another study introduced even more variables into the mix: quality of life, severity of SAHS, daytime sleepiness and psychologic functioning.⁵⁵ Here, participants with severe SAHS had reduced quality of life compared with matched control participants. One half of the SAHS patients also had elevated depression scores, and these depression scores were significantly correlated with quality of life. The investigators found no significant correlation between daytime sleepiness and quality of life, although there was a suggestion that there is a relationship between oxygen desaturation and quality of life.

Excessive daytime sleepiness (EDS), a concept that is both problematic and poorly defined,⁵⁶ is often assumed to be the result of disturbed or inadequate sleep.⁵⁷ Since SAHS is characterised by frequent arousals from sleep, it is assumed that EDS is a cardinal sign of SAHS. However, the association between EDS and severity of apnoea has been shown to be weak.⁵⁸ In view of reports in the literature indicating that the mechanism of EDS is multifactorial, one general population study simultaneously evaluated a wide range of potential risk factors associated with EDS.⁵⁹ The investigators used a logistic regression model to look at the relative contribution of various factors for the complaint of EDS. They found depression to be most strongly associated. The next most strongly related variables were obesity, diabetes, age and sleep duration.

Interestingly, the final variable, SAHS, did not make a significant contribution to the model, indicating that individuals with a complaint of

excessive daytime sleepiness should be adequately assessed for depression, obesity and/or diabetes even in the presence or absence of SAHS. Yet, this does not explain why successful treatment of SAHS, but not the adequate control of depression or diabetes, rapidly improves daytime sleepiness.⁶⁰

Treatment Aspects

Adherence Issues

CPAP is currently the treatment of choice in most cases of SAHS; however, treatment adherence rates are low.⁶¹ It would be useful if evaluations made at the point of diagnosis or at the initiation of treatment could identify patients likely to experience difficulties adapting to this demanding treatment.

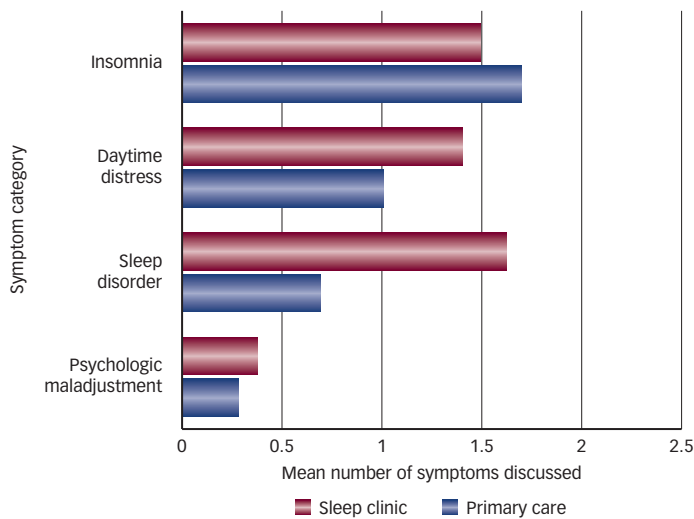
One study explored the concept of Type D (distressed) personality, defined as a combination of negative affect and social inhibition, and its potential role in CPAP adherence.⁶² It was found that the prevalence of Type D personality was 30 % in SAHS patients and that these patients reported a significantly higher frequency of troublesome side effects from CPAP treatment. Approximately 50 % of patients with Type D personality used their CPAP for less than four hours per night compared with 16 % of the non-Type D patients.

Another study investigated the extent to which psychological variables such as quality of life, psychopathology and patients' understanding of and attitude toward their illness and to the CPAP intervention influence adherence to CPAP treatment.⁶³ The investigators found that increased health-related symptoms or complaints predicted greater adherence to treatment, as did older age. On the other hand, maladaptive beliefs predicted non-adherence to treatment. The findings are interpreted to suggest that variables such as emotional state and beliefs are important in the prediction of CPAP use, indicating that interventions can be more effective if adapted to patients' subjective needs at a point before treatment is initiated. This may help explain the strong effect of behavioral interventions to improve CPAP adherence that are delivered prior to the initiation of CPAP therapy for SAHS.⁶⁴

Is Hypoxemia or Sleep Disruption in Sleep Apnea/Hypopnea Syndrome More Closely Related to Psychologic Distress?

There is evidence that depressive symptoms correlate with the degree of hypoxia in SAHS patients.⁴ There is also the possibility that repetitive sleep disruptions in SAHS have adverse effects on mood.⁶⁵ Improvement in psychologic symptoms has been reported as a result of CPAP treatment for SAHS.⁶⁶ Since the mechanism by which SAHS relates to symptoms of psychologic distress is unclear, one group of investigators tried to tease out the effects of correcting the respiratory disturbance (i.e. sleep disruption) from the effects of correcting oxygen desaturation (i.e. hypoxaemia).⁶⁷ They examined the effects of nocturnal oxygen supplementation and therapeutic CPAP treatment, compared with placebo CPAP, on general psychologic symptoms and on depressive symptoms in SAHS patients. They demonstrated that both the CPAP and the oxygen supplementation groups showed similar levels of improvement in psychologic distress, oxygen supplementation did not improve RDI scores and both the CPAP and

Figure 1: Mean Number of Symptoms Discussed by Primary Care and Sleep Clinic Patients with Their Physician



the oxygen supplementation groups improved on mean oxygen saturation. The investigators suggest that improvement in psychologic distress is driven by improved oxygen levels rather than by the frequency of apnoeic events or the number of arousals. Thus, lower levels of oxygen saturation may play a stronger role than sleep disruption in explaining the psychologic distress reported by individuals with SAHS.

Symptom Constellation Related to Identification of Individuals at Risk for Sleep Apnea

Prevalence of at least mild SAHS, particularly in the older population, is estimated to be between 20 and 60%.⁶⁸⁻⁷¹ Yet, referrals from primary care physicians for SAHS evaluations significantly under-represent the estimated population prevalence rates.^{72,73} Clearly, a substantial number of primary care patients have untreated symptoms, but either the constellation of presented symptoms are not being recognized as risk factors for SAHS or the problem lies with the patient-physician communication process.⁷¹

One study, carried out in our laboratory, set out to investigate what constellation of symptoms experienced and presented by the patient, and discussed with his or her physician, might lead to a 'successful' referral for further evaluation of possible SAHS. This study compared communication and referral patterns in primary care patients and patients who had already been identified as at risk for SAHS, as evidenced by having been referred to a sleep clinic for evaluation. We hypothesized that patients successfully identified as at risk for SAHS presented their symptoms in some uniquely salient manner, compared with primary care patients with similar symptoms who were not sent for further evaluation. The findings showed that while substantial numbers of older men and women patients in primary care reported experiencing a range of sleep disorder-related symptoms, relatively few had discussed these symptoms with their family doctor.

A subset of our sample endorsed more sleep-disorder symptoms than the rest of the sample. Many reported discussing these symptoms with their doctor, but still were not referred for further sleep disorder evaluation. When we compared scores of these primary care patients with scores of sleep clinic patients, the latter group appeared to get to the point more effectively. In spite of the fact that most primary care participants were found to have SAHS when evaluated in the sleep laboratory, it can be seen in *Figure 1* that they presented fewer specifically sleep disorder-related symptoms than did sleep clinic patients. Our findings suggest that some primary care patients who have significant SAHS complain of insomnia and daytime distress, rather than the more recognizable sleep disorder signs.

The Role of Fatigue

Daytime sleepiness has long been known to be a prominent aspect of SAHS,^{74,75} but recognition of the role of fatigue in sleep apnea is relatively recent.⁷⁶ One major problem in the whole domain of daytime sleepiness and fatigue has been the overlap in definition and lexicon between the concepts.⁷⁷ We addressed this problem by developing a technique to separate the constructs. This showed that the two symptoms were most clearly distinct when sleepiness is defined by sleep propensity and fatigue is defined as diminished energy or weakness.⁷⁸

In a very recent study⁷⁹ we identified four SAHS subgroups characterized by combinations of high and low levels of sleepiness and fatigue. Twenty-three per cent of the participants presented with high levels of both daytime fatigue and sleepiness, while a surprising 19 % were relatively asymptomatic on both of these variables. Ten percent experienced only high fatigue, and 8 % experienced low fatigue but high sleepiness. Clearly, SAHS has several symptom presentations, and fatigue is an important element, whether sleepiness is present or not. This study, which is one of the few to show that high fatigue in individuals with SAHS may be even more prevalent than high sleepiness, sampled a broad range of psychologic variables associated with high and low sleepiness and fatigue. These included almost all of the psychologic variables that had been explored in the studies we reviewed. It is clear from our results that highly fatigued individuals with SAHS reported many aspects of diminished quality of life and that they manifested less adaptive psychologic functioning in a number of domains, including depression and anxiety. Participants with SAHS who had low levels of sleepiness and fatigue were not significantly different from healthy controls. Notably, mean nocturnal oxygen saturation (SpO₂) also was lower in highly fatigued participants. In addition, nocturnal SpO₂, an important objective SAHS-related measure, was a significant predictor of self-reported fatigue but not sleepiness. The RDI, which measures number of respiratory disturbances per hour of sleep, was found to be a weak predictor of daytime sleepiness.

It is interesting that low mean SpO₂ is a disease characteristic found in another disorder—severe chronic obstructive lung disease (COPD)—where fatigue is also a prominent symptom.⁸⁰⁻⁸² In a study investigating COPD, when patients were divided into high and low fatigue groups (defined according to the Vitality subscale of the SF-36⁸³) the high fatigue group manifested both worse psychological adjustment as well as worse physical functioning and greater depression.⁸⁴

Conclusion

The recent data on fatigue and its associations raise the following possibilities for further study. Fatigue is an important, but relatively unrecognized, symptom in SAHS. Fatigue also may be a mediator for a range of psychologic and behavioral impairments, both in SAHS and in other conditions as well. Lower oxygen saturation may represent one potential physiological basis for the experience of fatigue. Since fatigue and low mean oxygen saturation are commonly associated with SAHS, but are not exclusive to this condition, it may be the

combination of low oxygen saturation and SAHS that underlies the assumed psychological manifestations of SAHS and other fatiguing disorders.

Neuroendocrine and inflammatory stress response systems are another subject of current research in terms of their role in the causes, consequences and correlates of SAHS. Further work to investigate these possibilities may yield important insights for the diagnosis and treatment of SAHS and its associated symptom constellation. ■

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