Chapter 8
Sleep-Disordered Breathing and Mental Illness

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Introduction

> Sleep that knits up the ravelled sleave of care, The death of each day's life, sore labour's bath, Balm of hurt minds, great Nature's second course, Chief nourisher in life's feast.
>
> Shakespeare, Macbeth

Magnitude and Scope of the Problem

Mental disturbance is extremely common among those who suffer from sleep disorders. Most psychiatric patients have sleep complaints, and a primary sleep disorder frequently also results in neuropsychiatric complications. Up to 2/3rd of patients who present to a sleep disorders center report an episode of depression within the previous 5 years, and one quarter described themselves as depressed at presentation [1].

Chronic sleep loss and sleep disorders impose an immense public health burden, and awareness among the general public and healthcare professionals remains low.

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It is estimated that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health. Insomnia is the most common sleep disorder, followed by sleep apnea and restless legs syndrome (RLS). Obstructive sleep apnea (OSA) is by far the most common form of sleep-disordered breathing, in which a person frequently stops breathing during his or her sleep. It results from an obstruction of the upper airway during sleep that occurs because of inadequate motor tone of the tongue and/or airway dilator muscles. More specifically, it is characterized by 'hypopneas' (decreases in breathing during sleep) or 'apneas' (actual pauses in breathing). Pauses in breathing during sleep of at least 10 seconds with obstruction of oronasal airflow despite continuous chest and abdominal movements are referred to as 'Obstructive Apneas' and are associated with a decrease in oxygen saturation and/or arousals from sleep [2]. Many patients with obstructive OSA also have central apneic episodes in which breathing stops temporarily but without any airway blockage or respiratory effort. Both kinds of episodes can cause harmful reductions in the level of oxygen in the blood.

OSA is a common sleep disorder prevalent in at least 2–4% of the adult population. The prevalence of OSA is increasing along with the epidemic of obesity in the USA. Risk factors for OSA include obesity, craniofacial abnormalities, upper airway abnormalities, heredity, smoking and nasal congestion. The core features of OSA include nocturnal hypoxemia, hypercapnia and sleep fragmentation with resultant excessive daytime sleepiness, mood problems, poor neurocognitive performance and potentially serious organ system dysfunction including a variety of adverse cardiovascular and metabolic effects. Some studies have suggested executive dysfunction in OSA patients, thought to be related to prefrontal lobe dysfunction caused by intermittent hypoxia. All of these conditions can seriously contribute to decrements in a patient's quality of life [2].

Mental disorders are highly prevalent in the general population and even more so among individuals with sleep disorders. Mood and anxiety disorders are associated with high rates of insomnia. Similarly, for many patients with sleep complaints, mental illnesses like depression and anxiety play an important role in their sleep complaints. Medications used for the treatment of mental illnesses can also play a significant role in the genesis or exacerbation of sleep complaint [3]. People with severe mental illness generally die sooner (in many cases as much as 25 years or more) compared with the general population, and this is primarily due to the high prevalence of physical illness, such as cardiovascular disease, rather than suicide. OSA plays a critical role in causing and exacerbating medical illnesses in these individuals. Thus, treating the general health of people with severe mental illness (including effective treatment of illnesses like OSA) is crucial [4].

Sleep disturbances are common in both mood and anxiety disorders. Some believe that there may be a bidirectional relationship between sleep disturbance and mental illnesses [3].

Some of the twentieth century's most devastating human and environmental health disasters have been attributed directly or indirectly to sleep loss, excessive sleepiness and fatigue-related performance failures including the tragedy at the Union Carbide chemical plant in Bhopal, India; the nuclear reactor meltdowns at

Three Mile Island and Chernobyl; and the grounding of the Exxon Valdez oil tanker.

The Clinical Significance of Obstructive Sleep Apnea

In addition to the considerable overlap between OSA and psychiatric illness, primarily depression and anxiety (addressed in the next section), OSA is also comorbid with multiple medical conditions. Research in the last 15 years has debunked the notion that chronic sleep deprivation has no health consequences apart from excessive daytime sleepiness [5]. Current research suggests that chronic sleep loss (less than 7 h a night) including sleep loss secondary to OSA has wide-ranging effects on the cardiovascular, endocrine, immune and nervous systems, including the following:

- Obesity in adults and children
- Diabetes and impaired glucose tolerance
- Cardiovascular disease and hypertension.

This is in addition to the negative effects of sleep loss on mental health which include anxiety symptoms, depressed mood and alcohol use.

Sleep Loss and Obesity

Obesity (defined as having a Body Mass Index (BMI) equal to or greater than 30 is now a major public health problem in developed nations and developing nations such as China and India are not far behind. It is well established that obesity is linked to multiple medical problems including increased risk of diabetes, heart disease, arthritis and cancer. Chronic sleep deprivation (less than 7 h per night) is one risk factor for obesity that has received increased attention in the last few years. The reduction in average sleep hours over the last three to four decades (with the widespread availability of television, video, computers, the internet, etc., as well as a rapid increase in the incidence of shift work) has coincided with the increase in the prevalence of obesity leading researchers to suspect a link between the two.

A recent study reported that the sleep duration of the average American adult has decreased to an average 6 h 40 min (weekdays/7 h 25 min-weekends) from 8.5 h in 1960 [6]. Chronic sleep loss can have a negative effect on appetite via two hormones that play a major role in appetite regulation: leptin, a satiety hormone produced by adipocytes and ghrelin, an appetite stimulant released by stomach cells. These chemicals exert opposite effects on appetite. Leptin levels are lower in the morning and rise gradually throughout the day. Leptin inhibits hunger during the overnight fast. Ghrelin levels decline immediately after meals and then rise

again after a few hours. Sleep exerts an inhibitory effect on ghrelin. In addition, sleep restriction leads to an increase in calorie consumption likely secondary to continued energy expenditure due to physical activity [7]. Obesity is one of the primary and more modifiable risk factors for development of OSA.

A number of studies suggest that reducing obesity will likely benefit sleep disorders, and treating sleep deprivation and sleep disorders may benefit individuals with obesity [7].

Sleep Loss and Impaired Glucose Tolerance

The link between obesity and diabetes is well established as is their long-term morbidity and mortality [8]. Recent studies have also pointed out the link between obesity, diabetes and chronic sleep deprivation [9]. It can be shown in healthy people that short-term sleep deprivation causes impaired glucose tolerance; thus, sleep might be essential for metabolic homeostasis. In addition, evidence is available that obstructive sleep apnea syndrome, narcolepsy and restless legs syndrome are all associated with impaired glucose tolerance or an increased incidence of diabetes [10, 11].

This association between impaired glucose tolerance and diabetes may partially explain the relationship between sleep loss and cardiovascular disease as discussed next.

Sleep Deprivation and Cardiovascular Disease

Several large epidemiological studies have documented the association between sleep loss and cardiovascular illness including myocardial infarction and possibly stroke. For sleep disorders such as OSA, the association is particularly strong since OSA has been proven to cause systemic hypertension, possibly myocardial infarction, congestive heart failure and stroke [12]. Several potential mechanisms for these phenomena have been suggested including autonomic, metabolic and inflammatory factors and oxidative stress. OSA results in sustained breathing efforts during pharyngeal collapse which leads to markedly negative intrathoracic pressure, hypoxemia and arousal from sleep. This leads to increased transmural cardiac pressure and ventricular afterload. Additionally, hypoxemia and repeated arousals from sleep lead to sympathetic surges increasing blood pressure and heart rate. Recurrent hypoxemia/reoxygenation cycles resemble ischemic events yielding reactive oxygen species such as peroxides and free radicals which promote atherosclerosis via a proinflammatory environment. Institution of CPAP (continuous positive airway pressure) can minimize or reverse many of these phenomena [13].

Clinical Observations About Sleep-Disordered Breathing and Psychiatric Illness

In the authors' experience, patients with psychiatric conditions are more vulnerable to develop OSA. There are several likely reasons for this. First of all patients with psychiatric disorders like schizophrenia and mood disorders are more likely to be obese which puts them at risk of development of metabolic syndromes. Secondly, many antipsychotic medications, antidepressants and mood stabilizers increase the risk of weight gain. In addition, depressed patients have low motivation to exercise and lead a healthy lifestyle, putting them at further risk of obesity and thus OSA.

Not all mental health clinicians are familiar with sleep-disordered breathing's comorbidity with psychiatric diseases, which poses an impediment in the care of these patients. Excessive daytime sleepiness is often attributed to either the illness or side effect of multiple medications patients are on.

Often patients with chronic psychiatric disorders have irregular sleep wake schedules, which confuses the clinical picture. Mental health clinicians might not pay attention to excessive daytime sleepiness as they feel that the symptoms are due to insomnia or medications.

There are studies suggesting that patients with depression and anxiety disorders including PTSD have poor adherence to CPAP [14]. Patients suffering from post-traumatic stress disorder (PTSD) are often claustrophobic and tend to prefer oral appliances. Systematic desensitization might help reduce feelings of anxiety with these patients. Educational and interactive groups focusing on adherence of CPAP might improve the use of CPAP as patients learn from their peers and see how others have been able to overcome non-adherence and benefitted from CPAP use.

The Prevalence of Depression and Anxiety in Obstructive Sleep Apnea

Population and Community Prevalence

Studies specifically designed to evaluate the prevalence of comorbid OSA and depression are few in number [15]. A recent large European survey (n = 18,980) reported a prevalence of major depressive disorder of 17% in patients with OSA or a sleep-related breathing disorder, while the prevalence for the whole sample was 4.3% [16]. In an even larger Veterans sample, this prevalence was found to be 21.8% in patients with OSA and only 9% in non-apneics [17].

This appears credible since the background prevalence of depression among people without OSA in these large-scale studies is consistent with earlier findings of 3–5% in community settings and 5–10% in primary care in the USA.

Older studies have reported higher rates of affective disorders in OSA (some up to 45%) and the risk seemed to rise in patients who were sleepier during the day

[18]. Those studies also found higher depression scores in patients with more severe OSA as indicated by a higher Apnea–Hypopnea Index (AHI).

Other smaller studies of severe OSA have reported very high prevalence of depression (in one study around 63%) [19]. It is impossible to draw any causal inferences from these data especially since the screening and diagnosis of depression in these studies are based on checklists and rating scales instead of in-depth clinical interview. Some of the overlapping symptoms of OSA and depression such as fatigue, decreased concentration, irritability and weight gain may confound the diagnosis.

An association between OSA and anxiety has also been documented. Data from the large Veterans study referenced above reveals a strong association between diagnosed sleep apnea and anxiety with 16.7% of OSA patients having comorbid anxiety and 11.9% with comorbid Posttraumatic stress disorder. Other studies have reported a relationship between nocturnal panic attacks and OSA [20].

Similarly, sleep problems are a central feature of PTSD, and this study strongly supports an association between sleep apnea and PTSD. Some authors have suggested that an arousal-based mechanism can promote the development of OSA after posttraumatic stress. There have been case reports and case series in which CPAP treatment of OSA improved insomnia, nightmares and PTSD symptoms [14].

Rates of Depression in Clinical Populations

Prevalence studies looking at people entering sleep clinics that were then diagnosed with OSA have shown high rates of depressive symptoms. One study found 41% of 167 Dutch sleep clinic referrals diagnosed with OSA according to American Sleep Disorders Association classification had a Beck Depression Inventory (BDI) score of 10 or more, indicating probable depression [21]. In a US study, sleep clinic depression rates among 406 people diagnosed with OSA were 30% overall (38% for women and 26% for men) [22].

Random selection of 130 women with ‘documented breathing disorders’ from a Canadian OSA clinical database showed 21% with a self-reported previous diagnosis of depression compared with 7% of 130 matched men from the same database [23].

Some variation in rates is to be expected with different clinical populations from different communities or when using different measures for depression. However, all of these studies report high rates of depression or depressive symptoms in people with OSA specifically women. Most of these studies, though, were not designed as prevalence studies. Therefore, this range is indicative of rates of depression in small clinical samples using variable inclusion/exclusion criteria. They cannot be generalized to people with OSA in populations nor can they be said to be indicative of the usual rates of depression in clinical OSA populations.

Obstructive Sleep Apnea and Mental Illness

OSA and Major Depression

Numerous studies have documented that OSA and depressive disorder are comorbid although some studies have questioned this correlation. There is a complex correlation between OSA and depression since there is considerable overlap between symptoms. The 'core' symptoms of OSA (such as snoring, snort arousals and witnessed apneas) differ clearly from some of the core symptoms of depression (such as sadness, anhedonia, guilt and agitation). However, there are a large number of symptoms common to both illness including fatigue, daytime sleepiness, poor concentration, irritability and weight gain. It is thus unclear whether depression is a primary consequence of OSA or whether some of these secondary symptoms of OSA such as sleepiness, sleep problems, irritability and social withdrawal manifest as a depressive syndrome. Current recommendations are that a mood disorder should be considered secondary to OSA and treated accordingly [24].

OSA and Anxiety

OSA has also been linked to anxiety and nocturnal panic attacks although the association between anxiety and OSA is not as well established as with depressive illness. Frequent awakenings due to choking from breathing cessations may play a role in the development of anxiety in OSA although this association is unproven. Studies have shown a correlation between anxiety disorders and one of the core symptoms of OSA, excessive daytime sleepiness (EDS) [25].

It has been suggested that anxiety may precede and potentially cause symptoms of EDS by contributing to insomnia and other sleep disturbances. This can be partially explained by the fact that anxiety disorders and the sleep wake cycle are regulated by several common neurotransmitters (e.g., Serotonin, γ-aminobutyric acid and neuropeptide Y). In a recent study, Rajesh et al. demonstrated MRI evidence of tissue injury in anxious patients with OSA versus patients with OSA but no anxiety [26]. This occurred in brain areas regulating emotion, and there was evidence indicating that many of these regions lay outside areas normally affected by OSA alone. This suggested additional injurious processes in anxious OSA subjects.

There is also an association between a family history of phobic disorders and EDS [24] as well as anxiety and chronic fatigue [27], another core symptom of OSA. Anxiety disorders are both highly prevalent and eminently treatable; therefore, these associations might have important clinical implications. In addition, OSA is highly prevalent in combat veterans with posttraumatic stress disorder who complain of being overly vigilant at night, nightmares, frequent awakenings and non-restorative sleep [28].

It is difficult to establish a clear correlation between sleep-disordered breathing and depression and anxiety symptoms. Lack of demonstrated relationship between OSA and psychiatric disorders does not necessarily mean there is no link between these conditions.

In most studies, there is lack of consistency with diagnostic criteria for OSA and for depression and anxiety. Most studies used clinical scales rather than diagnostic interviews to diagnose depression or anxiety. Most scales used for depression have sleep-related questions, either about hypersomnia or insomnia. Some authors suggested that questionnaires focusing on core symptoms of depression, like anhedonia or sadness, should be used in these studies [29].

In addition, confounding factors such as obesity, hypertension, diabetes and cardiovascular disease may impact the relationship between OSA and depression [30]. Both depression and OSA have independently been shown to be associated with metabolic syndrome and poor cardiovascular outcomes [31].

Studies suggesting a positive correlation between OSA and depression are summarized in Table 8.1, and studies suggesting no relationship between OSA and depression are summarized in Table 8.2.

Mechanisms

Pathophysiological Relationships

Sleep fragmentation and hypoxias a cause of depression.

The two major pathological events that occur in association in OSA with upper airway obstruction are: (1) fragmentation of normal sleep because of 'micro-arousals' occurring due to recurrent apneas and hypopneas leading to (2) recurrent, intermittent hypoxemia causing diminished saturation of oxyhemoglobin. These then lead to reduced daytime wakefulness, impaired cognitive function and low mood. Sleep fragmentation has been hypothesized as the principal cause of excessive daytime sleepiness (EDS) in OSA and patients with EDS and OSA are more likely to be depressed than patients with OSA without EDS [32].

Animal studies suggest that recurrent, intermittent hypoxemia, a central feature of OSA, is associated with a dose-dependent cell loss in the areas rich in noradrenergic and dopaminergic pathways important for both sleep/wake and mood regulation including the hippocampus and cortex. Concomitant depression can worsen neuronal injury accompanying OSA. Effective treatment of OSA with continuous positive airway pressure (CPAP) treatment leads to neuronal regeneration evidenced by gray matter volume increase in the hippocampus and frontal cortex volume [33]. This results in improvement in memory, attention and executive functions. Antidepressants have been shown to cause similar effects (increase in hippocampus volume via neurogenesis) [34].

Table 8.1 Studies suggesting a positive correlation

	Author/date	Population	Depression measures	OSA measures	Conclusions
Cross-sectional study	Enright/1996	5201 community sample of 65 year or older	CES-D	Self-reported Partner observed	Association in women, not in men
	Smith/2002	Records of 773 pts with OSA matched with controls	Physician diagnosis	Physician diagnosis	OSA pts OR of 1.4 past depression
	Aloia/2005	Sleep clinic sample of 93	BDI	RDI	Relationship of RDI and BDI total score and BDI somatic dimension. Independent relationship b/w RDI and somatic dimension for men
	Farney/2004	Records of >200,000 patients	Rx of antidepressant meds	Physician diagnosis	Likelihood of having OSA increased in depression
Cohort studies	Peppard/2006	1408 community patients (788 men)	Modified Zung depression scale or use of an antidepressant	PSG	1.8 odds ratio of developing depression in a 4-year interval as OSA develops or worsens. Dose–response relationship between severity of OSA and depression

Adapted from Harris et al. [15], with permission of Elsevier

OSA obstructive sleep apnea; *RDI* respiratory disturbance index; *CES-D* Clinical Epidemiological Scale for Depression; *BDI* Beck Depression Inventory; *SCL-90* Symptom Checklist-90; *HAD-D* Hospital Anxiety and Depression Scale; *SIGH-SAD-SR* Hamilton Depression Rating Scale-Seasonal Affective Disorders Self-Rating Scale

Table 8.2 Studies suggesting no correlation

First author/date	Study population	Depression measure	OSA measure	Conclusion
Kripke/1997	Community sample of 335	CES-D or items from SIGH-SAD-SR	Desaturations	No relationship
Pillar/1998	2271 referrals to a sleep clinic	SCL-90	RDI	No consistent relationship
Sforza/2002	44 OSA, 16 snorers	HAD-D	AHI, mean low oxygen saturation	No correlation b/w AHI and HAD-D, but with low O_2 sats

Adapted from Harris et al. [15], with permission of Elsevier
OSA obstructive sleep apnea; *RDI* respiratory disturbance index; *CES-D* Clinical Epidemiological Scale for Depression; *BDI* Beck Depression Inventory; *SCL-90* Symptom Checklist-90; *HAD-D* Hospital Anxiety and Depression Scale; *SIGH-SAD-SR* Hamilton Depression Rating Scale-Seasonal Affective Disorders Self-Rating Scale; *AHI* Apnea–Hypopnea Index

Neurotransmitter Disturbances

Obstructive sleep apnea is associated with elevated levels of the cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF). It has been hypothesized that these compounds are mediators of daytime sleepiness since administration of a tumor necrosis factor antagonist has been shown to dramatically reduce the level of daytime sleepiness in patients with OSA [35].

A vast body of literature has also documented the close association between major depression and the inflammatory immune response involving the proinflammatory cytokines IL-1, IL-6 and interferon [36]. While none of the studies are confirmatory for causation, they do suggest shared pathways between these conditions.

Further, obesity, particularly visceral obesity (a known risk factor for OSA), is also associated with an elevation in these cytokines [37].

Patients with OSA while awake are able to 'prop open' the upper airway through activation of the upper airway dilator muscles; when asleep, however, the neurochemical 'tonic' stimulation to upper airway motoneurons is lost as is muscle tone, resulting in pharyngeal collapse [38]. Abnormalities in central and peripheral neurotransmission of **Serotonin** have been implicated as a potential cause of major depression. It is now established that during wakefulness Serotonin, most probably acting through 5-HT2A receptors, provides a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway dilating muscles. It is hypothesized that withdrawal of this serotonergic input during sleep might predispose to airway obstruction in the form of apnea or hypopnea [38, 39]. If we conceptualize a central pathology in OSA as easy upper airway collapsibility during

sleep, then anything decreasing the activation of upper airway dilator muscles during sleep can potentially cause the disorder. The activation of Serotonin receptors innervating the genioglossus and other upper airway dilator muscles, particularly 5-HT2A receptors, is excitatory. The release of Serotonin from the raphe neurons steadily declines with the transition from wakefulness to NREM sleep and is minimal during REM sleep. Thus, loss of 'tonic' serotonergic activity is one potential basis for the reduced upper airway muscle activation and increased collapsibility of the upper airway characteristic of OSA [38, 39]. However, this pathway is extremely complex, with multiple receptor subtypes, and there may be other pathways shared with other neurotransmitters.

Norepinephrine has several similarities with Serotonin as a neuromodulator of motoneuronal function although studies suggest that its role is complementary [38]. Hypoxia secondary to OSA also alters motoneuronal and extracellular levels of the purines **Adenosine and ATP**, specifically reducing ATP and increasing Adenosine. Adenosine injected into the hypoglossal nucleus suppresses hypoglossal motoneuronal activity. This association needs to be explored further [38].

A similar inhibition of hypoglossal nerve activity is observed with **Acetylcholine** (ACh) which targets two specific groups of receptors: muscarinic and nicotinic. Activation of the muscarinic receptors inhibits hypoglossal and can be blocked with atropine, a muscarinic antagonist. This likely occurs via presynaptic suppression of glutamate release. ACh also causes excitation through activation of nicotinic receptors that is masked by the overwhelming muscarinic effect [38].

In addition **GABA and glycine** are the primary inhibitory neurotransmitters acting at these areas. Glycine plays an essential role in REM sleep postural atonia. However, the actions of these neurotransmitters on hypoglossal muscles are still under debate [38]. In one study, strychnine, a glycine antagonist, completely abolished apneas and regulated ventilator effort in OSA [40].

Hypocretin (orexin-A) increases electromyographic activity in the genioglossus muscle and reductions in orexin in upper airway motor nuclei in NREM sleep could contribute to the suppression of upper airway dilator activity in NREM sleep [38].

In addition to the above, a number of lesser studied neuropeptides modulate brain stem motoneuron activity. Many of these have significant excitatory effects, e.g., **Vasopressin** binds to the V1A receptor on facial and hypoglossal motoneurons [41]. It may play a greater role in newborns as the receptor density declines with age [42].

There is binding of **Substance P** to the NK-1 receptor in the hypoglossal nucleus, and this declines with recurrent hypoxia [43]. Substance P (NK-1) agonists have been shown to be excitatory [44]. Hypoglossal motoneurons also possess **Oxytocin** binding sites [45], but their physiological significance is currently unknown. **Histamine** activity is also increased in the brain while awake and it is thus excitatory [38]. There may be more, as yet undiscovered substances that may have additional roles to play.

Hormonal Factors

Hormonal factors may also influence the activity of upper airway muscles. The genioglossal musculature in younger women is highly active compared to postmenopausal women and men of the same age. Thus, progesterone might be protective against sleep apnea. Exogenous progesterone administration has been shown to improve ventilation during sleep in men and women with sleep apnea [46]. Estrogen administration has been shown to decrease plasma levels of interleukin-6, which are higher in patients with sleep apnea [47]. Thus, postmenopausal women undergoing hormone replacement therapy (receiving progesterone and estrogen, both protective against OSA) have lower rates of OSA.

On the other hand, the exogenous administration of testosterone in women and healthy men can induce sleep apnea secondary to greater upper airway collapsibility independent of weight gain [48]. One cause might be greater deposition of soft tissue in the pharynx causing relaxation of the pharyngeal dilator muscles. This can because of redistribution of body fat under the influence of testosterone. This usually resolves if the exogenous testosterone is withdrawn.

Testosterone can also play a role in central apneas by altering the sensitivity of the central chemoreceptors to $PaCO_2$ [49].

Obese young females with polycystic ovary syndrome (POS) (who generally have higher circulating levels of androgens) develop sleep apnea at a higher rate than controls, and women with OSA have a higher level of circulating androgens hormones than do normal women paired by age and weight [48].

Thus, in relations to OSA, female hormones are protective and vice versa for male hormones.

Impact of Treatment

(a) Impact of treatment of OSA on depression and anxiety

CPAP treatment improves daytime sleepiness in patients with OSA. In clinical studies, improvement in daytime sleepiness often translates into improvement in the depressive and anxiety symptoms as most mood and anxiety scales have sleep-related questions.

The effect of CPAP on mood and anxiety is inconsistent. In a systematic review of 26 studies [50], nine evaluated the effects of CPAP on psychological status. Six of the studies used a comparison group for CPAP treatment other than pretreatment status. Three studies showed an overall improvement in psychological performance.

In the same review, eight studies looked at the effects of CPAP on depression. Five showed significant improvement, and none showed worsening. The authors concluded that CPAP has significant and positive impact not only on symptoms of sleepiness, but also on depressive symptoms.

In another review [51] the authors included studies in which patients were diagnosed with polysomnography for OSA and then subsequently treated for at least 3 months with CPAP. Various scales were used to evaluate for depression and anxiety. Four out of seven studies showed significant improvement in depression and anxiety.

Sanchez et al. [52] looked at randomized clinical trials in which CPAP was compared with more conservative measures like sham CPAP, oral appliances and placebos. In this review, five out of seven studies showed reduction in depressive scores with the use of CPAP. Comparison of CPAP with sham CPAP conducted by Yu et al. [53] showed significant reduction in mood scores (POMS (Profile of Mood States), except vigor subscale), which were not treatment specific, suggesting a placebo effect. Other authors reported significant lower depression scores (POMS and Hospital Anxiety and Depression Scale (HADS)) after CPAP treatment as compared with a control group [54, 55].

Published reports also show negative findings, suggesting that improvement of mood may not be clearly related to treatment of OSA. For example, Barnes et al. [56] compared CPAP with oral placebo and did not find significant difference between the two groups in quality of life and POMS and Beck Depression Inventory (BDI).

Engelman et al. [57] found no differences between CPAP and oral placebo on HAD scales.

There are discrepancies with regard to prevalence of anxiety and depression in patients with OSA. Although OSA is more common in men, various studies suggest that women have (or report more) depression than men [58].

Most authors suggest that treatment of OSA has an overall beneficial effect on quality of life and mood. The improvement in 'depression' may imply that CPAP is having an effect on epiphenomena such as fatigue, sleepiness and motivation rather than depression.

Impact of Treatment of Depression and Anxiety on OSA and CPAP Adherence

In some cases, treatment of comorbid insomnia and anxiety with a benzodiazepine and hypnotic may worsen OSA. These medications may decrease muscle tone in the already functionally impaired upper airway dilator muscles, blunt the arousal response to hypoxia and increase the arousal threshold for an apnea event, therefore increasing the number and duration of apneas [59].

Depression is known to have an effect on adherence to treatment of chronic medical conditions like cardiovascular disease, and treatment of depression tends to improve acceptance and compliance. Depressed patients might have poor adherence to CPAP use, suggesting that depression should be treated aggressively in these patients [60].

Patients with anxiety disorder, particularly with posttraumatic stress disorder (PTSD), have worse adherence to CPAP [61]. These patients complain of claustrophobia feelings with the use of CPAP. In some cases treatment of OSA improves subjective nightmares by reducing sleep fragmentation. Behavioral treatments like relaxation training and systematic desensitization can help some individuals get used to CPAP despite the feelings of claustrophobia [62].

Adherence to CPAP varies. In a pre/poststudy of 54 newly diagnosed OSA patients, neither pre-CPAP depression scores nor post-CPAP improvement in these scores were related to CPAP adherence [63].

In another study [64], depressive scores predicted poor CPAP adherence. Treatment of depression might improve acceptance of CPAP, reduce excessive sleepiness and improve quality of life, but this remains to be confirmed.

Central Sleep Apnea

Central sleep apnea (CSA) is characterized by cessation of airflow without respiratory effort. This is in contrast to obstructive sleep apnea, in which respiratory effort is present during breathing cessation.

In CSA, there are repetitive episodes of decreased ventilation due to complete or partial reduction in central neural outflow to the respiratory muscles. Congestive heart failure and dwelling at high altitudes are classical conditions in which CSA is present. Moreover, opiate pain medications also suppress breathing centers in the medulla and can cause CSA [65]. There are no studies looking at the relationship between CSA and psychiatric disorders or relationship of CSA caused by opiate pain medications and depression.

Hyperventilation syndrome is a behavioral condition in which minute ventilation exceeds metabolic demands, resulting in hemodynamic and chemical changes that produce dysphoric symptoms. Hyperventilation syndrome is frequently caused by anxiety and panic disorder. Behavioral hyperventilation, which is associated with anxiety, has been postulated to trigger CSA in three cases [66].

It is thought that patients who develop CSA have hypersensitive chemoreceptors, which respond briskly to increased CO_2 in the blood, resulting in overcompensating with hyperventilation and thus overshooting the apnea threshold [65]. In one study, authors found that children with congenital central hypoventilation, in which there is lack of chemoreceptor responsiveness to CO_2, have decreased anxiety rates. This might suggest that hypersensitive chemoreceptivity might be related to anxiety, though there are no studies available looking at this relationship [67]. With more attention to CSA and complex sleep apnea (central apneas triggered by CPAP therapy), we hope there will be studies looking at this possible complex relationship between anxiety, depression and central sleep apnea.

In the authors' clinical practice, most patients with CSA have insomnia and excessive daytime sleepiness, which could mimic symptoms of depression.

Effects of Sleep Loss on Mental Health

Sleep loss (referring, in general to less than 7–8 h per night) is highly prevalent and continues to worsen, as a result of both social factors (shift work, the availability of television, internet, etc.) and biological factors such as advancing age. The main symptom of sleep loss is excessive daytime sleepiness, but other symptoms include depressed mood and poor memory or concentration [68]. Chronic sleep loss can have serious consequences for health, performance and safety. It has been estimated that the percentage of men and women who sleep less than 6 h has increased significantly over the last 20 years [69]. Chronic sleep deprivation and sleep disruption affect a wide range of body systems.

Neuroendocrine and Hormonal Effects

Sleep disruption is a stressor and, like all stresses, activates the body's established stress–response systems: the autonomic sympathoadrenal system and the hypothalamic–pituitary–adrenal (HPA) axis system [70]. This causes significant disruption of cortisol and adrenocorticotrophic hormone (ACTH) levels. Numerous studies have reported a higher prevalence of obesity, impaired glucose tolerance and diabetes in subjects with partial or total sleep deprivation after controlling for age, Body Mass Index (BMI) and other confounders [71].

Changes in the serum levels of both growth hormone [72] and prolactin [73] have also been documented in patients with OSA. Thyroid activity, including TSH, T3 and T4 levels is increased by sleep deprivation [74]. In general, sleep appears to suppress stress systems and results in lower plasma levels of stress hormones such as cortisol and adrenaline.

Behavioral/Cognitive/Mental Health Effects

Excessive sleepiness, fatigue, irritability and decrease in concentration have been documented as the effects of sleep deprivation. In addition longer reaction times, poor short-term memory, reduced motivation, distractibility and poor performance are also associated with both sleep deprivation and sleep fragmentation [75].

Even if the total sleep time remains the same, fragmentation of sleep (such as occurs in OSA) has been shown to impair functioning including reduced vigilance and reaction times [75]. OSA causes chronic sleep deprivation as well as changes in normal sleep architecture. This results in numerous cognitive problems including deterioration in memory, intellectual capacity and motor coordination as well as a decline in psychomotor vigilance. In addition, it can result in personality changes, irritability, depressive symptoms and an increased proneness to accidents [76].

The relationship between sleep disorders and psychiatric illness is bidirectional. Psychiatric disorders and their treatment can cause or contribute to sleep problems, and psychiatric illness can also be a consequence of sleep disorders [14]. Effective treatment for OSA has been shown to improve mood symptoms [32].

Conclusion

Clinicians must consider depression and anxiety disorders as comorbid conditions in every patient with OSA. Patients with depression and anxiety might present with sleep-related complaints such as insomnia, fragmented sleep, or daytime sleepiness. The sedative effects of psychotropic medications can often mimic the residual symptoms of daytime sleepiness in patients with OSA.

As OSA is associated with a higher prevalence of psychiatric comorbidities, patients with residual symptoms of daytime sleepiness and fragmented sleep should be screened for depression and anxiety so they could be appropriately referred for treatment of their psychiatric condition.

CPAP adherence is poor in patients with depressive and anxiety disorders. Attention to barriers to the use of CPAP is important in these patients as it might improve adherence.

Psychiatric illness exists in close conjunction with sleep disorders. Comorbid mental illness and sleep disorders increase disease burden and produce adverse long-term outcomes. Patients with sleep disorders need to be screened carefully for psychiatric illness and, where necessary, concomitantly treated for comorbid psychiatric illness.

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