REVIEW

# Obstructive Sleep Apnea and Depression: A Review

**by SHAKIR M. EJAZ, MD; IMRAN S. KHAWAJA, MD; SUBHASH BHATIA, MD; AND THOMAS D. HURWITZ, MD**

*Dr. Ejaz is from the Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, Minnesota, and University of Minnesota, Minneapolis, Minnesota; Drs. Khawaja and Hurwitz are from Veterans Affairs Medical Center, Minneapolis, Minnesota, and University of Minnesota; and Dr. Bhatia is from the VA Medical Center, Omaha, Nebraska.*

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**ADDRESS FOR CORRESPONDENCE:** Imran S. Khawaja, MD, One Veteran's Drive, VA Medical Center, Minneapolis, MN 55417; Phone: (612) 629-7447; E mail: khimran@yahoo.com

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## ABSTRACT

Obstructive sleep apnea is a common sleep disorder associated with several medical conditions, increased risk of motor vehicle accidents, and overall healthcare expenditure. There is higher prevalence of depression in people with obstructive sleep apnea in both clinical and community samples. Many symptoms of depression and obstructive sleep apnea overlap causing under-diagnosis of obstructive sleep apnea in depressed patients. Sleep problems, including obstructive sleep apnea, are rarely assessed on a regular basis in patients with depressive disorders, but they may be responsible for antidepressant treatment failure. The mechanism of the relationship between obstructive sleep apnea and depression is complex and remains unclear. Though some studies suggest a mutual relationship, the relationship remains unclear. Several possible pathophysiological mechanisms could explain how obstructive sleep apnea can cause or worsen depression. Increased knowledge of the relationship between obstructive sleep apnea and depression might significantly improve diagnostic accuracy as well as treatment outcomes for both obstructive sleep apnea and depression.

## INTRODUCTION

Obstructive sleep apnea (OSA), the most common subtype of breathing disorders of sleep, is a highly prevalent and underdiagnosed disease. The prevalence in the general population is approximately 20 percent if defined as an apnea hypopnea index (AHI) greater than five events per hour (the AHI is the number of apneas and hypopneas per hour of sleep).[1] An AHI of less than five is considered normal, 5 to 14 is mild OSA, 15 to 29 is moderate OSA, and 30 and above is severe OSA. Vulnerability to excessive daytime sleepiness (EDS) with increasing severity of AHI varies and a high AHI does not necessarily mean worsening of EDS. OSA increases the risk for poor neurocognitive performance and organ system dysfunction, due to repeated arousals and/or intermittent hypoxemia during sleep over months to years. The severity and duration of OSA necessary for development of these outcomes likely varies among individuals. In addition, there is an increased risk of mortality in patients

**TABLE 1.** Known adverse clinical outcomes of obstructive sleep apnea

| OUTCOMES | SUMMARY |
|---|---|
| All cause mortality | Patients with untreated severe OSA (AHI≥30) appear to have a 3- to 6-fold increased risk of all-cause mortality compared to individuals without OSA.[2,4,5] |
| Cardiac disease | OSA is associated with systemic hypertension, mild pulmonary hypertension, coronary artery disease, cerebrovascular disease, cardiac arrhythmias, and ischemic stroke.[6–8] Untreated OSA may also be associated with the development of heart failure in men, particularly in those who have AHI≥30 events per hour of sleep.[7] |
| Neurocognitive function | OSA induces excessive daytime sleepiness, inattention, and fatigue, which impairs daily function, induces or exacerbates cognitive deficits, and increases the likelihood of errors and accidents.[1,9] |
| Motor vehicle accidents | Motor vehicle crashes are more common among patients with OSA than without OSA, and may have a greater impact on morbidity and mortality than the cardiovascular complications of OSA.[9] |
| In-hospital mortality | Patients with a combination of obesity, polycythemia, hypoventilation, hypersomnolence, and sleep apnea have high in-hospital mortality from cardiorespiratory failure, pulmonary embolism, and renal failure.[6] |
| Perioperative complications | Patients with OSA have greater perioperative complications from intubation difficulties and impaired arousal from sedatives.[10] |
| Healthcare burden | Patients with OSA utilize more medical resources and have greater medical disability than individuals without the disease.[4–6, 11–13] |

OSA: obstructive sleep apnea; AHI: apnea hypopnea index

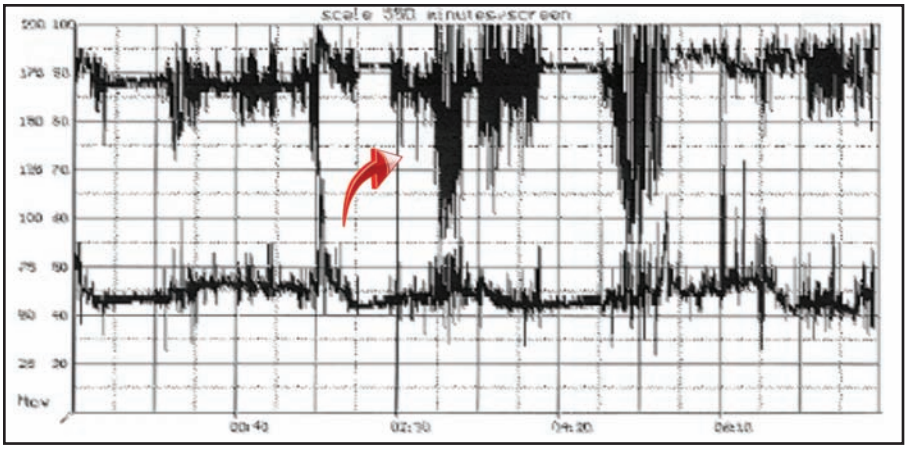

**FIGURE 1.** Overnight pulse oximetry testing. Mean oxygen saturation: 88%; minimum saturation 60%; number of events with desaturation >4%=95. Arrow indicates severity of desaturation in clusters, suggesting sleep-stage-dependent worsening of respiratory function.

with consequences of hypertension and cardiovascular risks, especially if their AHI is greater than 30 events per hour of sleep.[2]

The most common and effective treatment for OSA is continuous positive airway pressure (CPAP) therapy, which splints the pharyngeal airway space leading to improved oxygenation and decreased sleep fragmentation. It is considered to be the first line of therapy for this disorder.[3] Table 1 emphasizes the current medical implications of OSA supported by published literature to date.[2,4–13]

## CLINICAL VIGNETTE

A 50-year-old Caucasian man with a past medical history of obesity, diabetes, and hypertension presented to the psychiatry clinic with depressed mood nearly every day for more than two weeks. The patient also expressed diminished interest in activities and noted significant weight gain in the past year. Psychomotor retardation had been noticed by others. The patient also endorsed sleep maintenance insomnia as well as fatigue and sleepiness during the day. He reported difficulty with memory and concentration. His Patient Health Questionnaire-9 (PHQ-9)[14] score was 23 (a score of >10 indicates depression) at first visit. On physical examination, the patient had a body mass index (BMI) of 30kg/m$^2$ and a neck circumference of 19 inches. Mood was depressed and affect appropriate. Initial diagnosis was major depressive disorder (MDD) and therapy was initiated with paroxetine 20mg/day.

Four months later, the patient described some improvement in depression and his PHQ-9 score was 18. He continued to complain of daytime fatigue, somnolence, psychomotor retardation, and poor concentration. On further questioning, he endorsed symptoms of snoring that "shook the house" as well as apneas and snort arousals during sleep that were witnessed by others. His Epworth Sleepiness Scale (ESS)[15] score was 18 on a scale of 0 to 24 (a score >10 is considered sleepy). Overnight pulse oximtery performed revealed remarkable desaturations of oxyhemoglobin reaching a nadir of 60 percent during sleep (Figure 1). Subsequent polysomnography (PSG) revealed severe OSA with AHI of 95/hour, corrected by CPAP at 10cm of $H_2O$ pressure.

During the months following initiation of nightly CPAP therapy, he

described remarkable improvement in his depression, stating that he never felt better in his life. The patient was able to taper off paroxetine and maintain improvement in his mood and alertness while using CPAP.

## SLEEP APNEA AND DEPRESSION

The relationship between depression and OSA is complex. Figure 2 shows diagnostic symptoms of OSA from the *International Classification of Sleep Disorders, Second Edition* (ICSD-2) and for MDD from the *Diagnostic and Statistical Manual for Psychiatric Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) and *Principles and Practice of Sleep Medicine*.[16–18] Because of the shared symptoms, a checklist approach to diagnosis could lead to misdiagnosis.

Depression and neurocognitive disorders have been associated with OSA,[19–22] though the pathophysiology remains elusive. To clarify the current understanding of this association, we conducted a review of relevant published literature.

## METHODS

A Medline search was conducted on literature published between 2000 and 2011 using the following key words: "depression," "OSA," "sleep apnea," "mood disorders," and "CPAP." If not explicitly tabulated, data were extracted from tables and figures. Papers reporting on the relationship between OSA and depression, especially the prevalence of depression in OSA, effects of CPAP on mood, and possible pathophysiological relationships were sought. We observed that there was substantial variability of study designs.

In the literature, *obstructive sleep apnea* was described as sleep apnea, sleep-related breathing disorder, and obstructive sleep apnea syndrome (OSAS). For the purpose of this review, we used "OSA," which is inclusive of all obstructive sleep apneas with the exception of central apneas and Cheyne-Stokes breathing.

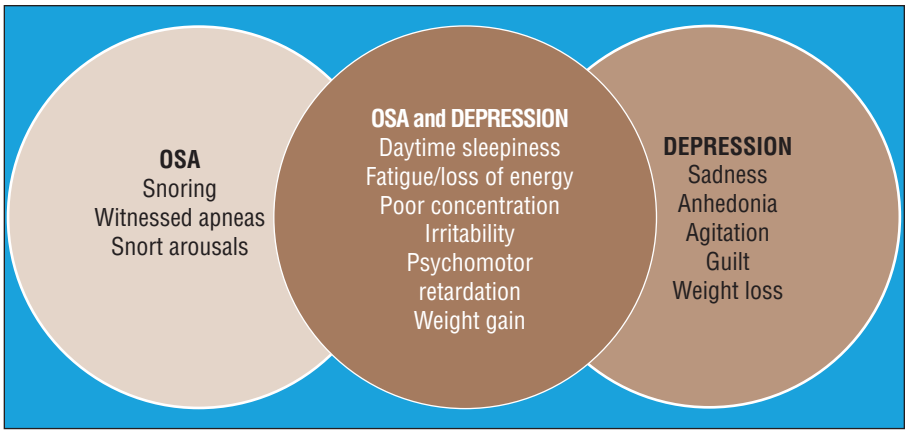


**FIGURE 2.** Overlapping symptoms of obstructive sleep apnea (OSA) and major depression. Adapted from: American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Second Edition, Diagnostic and Coding Manual.* Westchester, IL: American Academy of Sleep Medicine; 2005;[16] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000;[17] and Kryger, MH, Roth T, Dement WC (eds). *Principles and Practice of Sleep Medicine, Fourth Edition.* Philadelphia, PA: W.B. Saunders; 2005.[18]

In addition, "depression" was used to represent depressive symptoms rather than depressive disorders. Most studies used various scales/questionnaires rather than diagnostic interviews based on *DSM-IV-TR* to diagnose depressive disorder(s). Therefore, we used depression in a broader sense to cover the full spectrum of depressive disorders.

## RESULTS

**Prevalence of depression in patients with OSA.** The prevalence of depression in patients with OSA ranges from 5 to 63 percent, according to our literature search. Depression reported is of variable severity, diagnosed by clinical questionnaires for mood disorders or on the basis of clinician observation or the patient's self-reported symptoms. These questionnaires included, but were not limited to, the Beck Depression Inventory[23] (BDI), Minnesota Multiphasic Personality Inventory[24] (MMPI), Center for Epidemiological Studies Depression Scale[25] (CES-D), Hospital Anxiety and Depression Scale[26] (HADS), the Profile of Mood States[27] (POMS), and the Zung Depression Rating Scale[28] (ZDRS).

In a large, retrospective review of the Veterans Health Administration data bank, 118,105 patients out of 4,060,504 had a diagnosis of OSA (estimated prevalence of 2.91%).[19] Mean age at time of diagnosis was 57.6 years. Psychiatric diagnoses in the OSA group included depressive disorders (21.8%), anxiety disorders (16.7%), posttraumatic stress disorder (11.9%), psychotic disorders (5.1%), and bipolar disorders (3.3%). Psychiatric diagnoses were obtained from the electronic records. In comparison to depressive disorders with a 21.8-percent rate, the combined rate of anxiety disorders was 28.6 percent. Prevalence of depression in patients with OSA was higher as compared to patients without OSA (21.8 vs 9.43%, respectively [$P<0.0001$]). An earlier study by Guilleminault et al[29] reported that among 25 male patients with OSA, 24 percent had previously seen a psychiatrist for anxiety or depression. In 1984, Reynolds et al[30] studied male patients with OSA, and an estimated 40 percent met the research diagnostic criteria for an affective disorder, with a higher risk of depression in those patients who were sleepier during the day. In 1989, Millmann et al[31] reported that among 55 patients with OSA, 45 percent had depressive symptoms on the ZDRS. The group of patients scoring higher on ZDRS for depression also had a significantly higher AHI. In a multinational European study[32] of

18,980 subjects, which were representative of the general population in five different countries (United Kingdom, Germany, Italy, Portugal, and Spain), researchers conducted a telephone survey. The survery showed that 17.6 percent of subjects with a breathing-related sleep disorder diagnosis also met *DSM-IV-TR* criteria for MDD. They also found that about 18 percent of individuals with a diagnosis of MDD had a breathing-related sleep disorder. The prevalence of MDD in the group without breathing-related disorder was 4.3 percent. The odds ratio of sleep-disordered breathing in patients with MDD was 5:26 in comparison to those in the general population even after controlling for obesity and hypertension.

Other smaller studies of severe OSA have reported similar findings. Schwartz et al[33] found a 50-percent prevalence of depression as measured by the BDI scale in 50 patients with OSA. Yamamoto et al[34] found that among 41 patients with severe OSA, 63 percent reported depression utilizing ZDRS. The prevalence rates of depression in patients with OSA reported in these studies are much higher than anticipated in the general population without OSA.

In contrast, Phillips et al,[35] in a five-year, longitudinal study of elderly patients with mild OSA, reported no difference in prevalence of depression when compared to individuals presumed to be without OSA. The limitations of this study include small sample size, older age of patients in OSA group, comparison of OSA data five years earlier, and higher attrition rates.

In another large-scale study, Pillar and Lavie[36] used Symptom Checklist 90[37] (SCL-90), a screening rather than diagnostic tool. In a study of 2,271 patients (predominantly men), they found no relationship between OSA and depression. Since most studies used scales and screening instruments instead of clinical interviews to diagnose depression, it is difficult to evaluate the relationship between OSA and clinical depression. This may reflect a phenomenon of vital exhaustion (i.e., cognitive and somatic symptoms without affective symptoms prevalent in various medical disorders and depression states).

## THE RELATIONSHIP BETWEEN OSA AND DEPRESSION

There may be several reasons for the absence of relationship between OSA and depression. Lack of demonstrated relationship does not necessarily mean that there is no link between the two conditions. For instance, severity of depression is not necessarily related to the number of symptoms but to severity of these symptoms as measured by various scales. Also, variability in this relationship could be due to genetic susceptibility and variation.[38] Vulnerability to EDS with increasing AHI varies considerably and not all patients who have OSA as defined by AHI have EDS.[39] Our review suggests variability of diagnosis standards in depression and OSA literature.

Despite limitations of some studies, there is a higher rate of depression in patients with OSA compared to patients without OSA. However, correlation does not establish a cause-and-effect relationship. This relationship could be coincidental or due to fragmentation of sleep or repeated episodes of hypoxia.

In addition, confounding factors, such as obesity, hypertension, diabetes, and cardiovascular disease, may impact the relationship between OSA and depression. Both MDD and OSA have independently been shown to be associated with metabolic syndrome and with the development of cardiovascular disease.[40,41] In particular, insulin resistance may contribute to the pathophysiology of depressive disorder and has been proposed to underly the association between depression and cardiovascular disease,[42] similar to that with OSA.

Studies exploring the relationship between OSA and depression are summarized in Tables 2 and 3.[36,43–49] Except for one prospective study, the majority of the studies listed are retrospective and cross-sectional in nature using variable instruments and scales for measurement of depression. The conclusions of these studies are also variable; therefore, a true comparison between studies is rather difficult.

**Pathopysiological relationships.** *Sleep fragmentation and hypoxia as a cause of depression.* Two major phenomena occur in association with upper airway obstruction in OSA: 1) sleep fragmentation occurs by way of recurrent neurophysiological arousals due to apneas and hypopneas; and 2) intermittent hypoxemia is a consequence of subsequent temporary drops of circulating oxygen, manifested by diminished saturation of oxyhemoglobin.[50] These are likely to impact maintenance of daytime wakefulness, cognitive function, and mood. Stepanski et al[51] suggested that sleep fragmentation was the principal cause of EDS in OSA. More recently, Ishman et al[52] reported that patients with OSA and EDS are more likely to be depressed than patients with OSA without EDS. It can be conceptualized that disturbance of the sleep/wake cycle is often present in both OSA and depression. Several excitatory and inhibitory neurotransmitters like serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) are implicated in both wakefulness and regulation of mood.

In a study by Bardwell et al,[53] there was no relationship between either sleep fragmentation or hypoxemia in patients with EDS when the effects of BMI and hypertension were statistically considered as possible co-factors. The authors published another study[54] comparing the effects of oxygen, CPAP, and placebo in 38 patients with OSA. In this randomized trial, oxygen treatment was associated with a significant reduction in psychological symptoms of depression. The authors suggested hypoxemia may play a stronger role than sleep fragmentation in influencing depressive symptoms.[54]

Nightly, recurrent, intermittent hypoxemia, a feature of OSA, has been studied in animal models. It has been

**TABLE 2.** Studies describing a relationship between OSA and depression

| | AUTHOR/ DATE | STUDY POPULATION | TYPE OF STUDY | DEPRESSION MEASURES | OSA MEASURES | CONCLUSIONS |
|---|---|---|---|---|---|---|
| CROSS-SECTIONAL STUDIES | Enright[43] 1996 | 5,201 community sample of ≥65 years old | Retrospective | CES-D | Self-reported; partner observed | Association in women, not in men |
| | Smith[44] 2002 | Records of 773 patients with OSA matched with controls | Retrospective | Physician diagnosis | Physician diagnosis | OSA patients odds ratio of 1.4 past depression |
| | Aloia[45] 2005 | Sleep clinic sample of 93 patients | Retrospective | BDI | RDI | Relationship of RDI and BDI total score and BDI somatic dimension. Independent relationship between RDI and somatic dimension for men |
| | Farney[46] 2004 | Records of >200,000 patients | Retrospective | Prescriptions of antidepressant medications | Physician diagnosis | Likelihood of having OSA increased in depression |
| COHORT STUDIES | Peppard[47] 2006 | 1,408 community patients (788 men) | Prospective | 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 M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev.* 2009;13(6):437–444.
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 3.** Studies describing no relationship between OSA and depression

| AUTHOR/ DATE | STUDY POPULATION | TYPE OF STUDY | DEPRESSION MEASURES | OSA MEASURES | CONCLUSIONS |
|---|---|---|---|---|---|
| Kripke[48] 1997 | Community sample of 335 patients | Retrospective | CES-D or items from SIGH-SAD-SR | Desaturations | No relationship |
| Pillar[36] 1998 | 2,271 referrals to a sleep clinic | Retrospective | SCL-90 | RDI | No consistent relationship |
| Sforza[49] 2002 | 44 OSA patients, 16 snoring patients | Retrospective | HAD-D | AHI, mean low oxygen saturation | No correlation between AHI and HAD-D, but with low $O_2$ saturation |

Adapted from: Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev.* 2009;13(6):437–44.
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

associated with dose-dependent cell loss in the areas rich in noradrenergic and dopaminergic pathways important for both sleep/wake and mood regulation.[55] Furthermore, preliminary neuroimaging data suggest that depression may worsen neuronal injury accompanying OSA and may expand damage in regions controlling affect and cognition.[56] Zimmerman et al[57] reviewed neuroimaging studies of OSA and found mixed support for structural abnormalities but concluded that there is converging evidence of hippocampus atrophy and white matter changes, particularly in the frontal lobes.[57] A more recent study by Canessa[58] found improvement in memory, attention, and executive functions that correlated with grey matter volume increase in the hippocampus and frontal cortex volume in patients with OSA after treatment with CPAP. Authors concluded that cognitive and structural deficits in OSA may be secondary to sleep deprivation and repetitive intermittent hypoxemia and that the negative effects may be recovered by treatment with CPAP.[58] Antidepressants have also been shown to increase hippocampus volume via neurogenesis in depressed patients.[59]

*The role of serotonin in the neurobiology of depression and upper airway control in OSA.* Serotonin has been implicated in depression.[59] Serotonin also influences upper airway dilator motor neurons through the hypoglossal nucleus, which is further reduced in sleep states.[58] Abnormalities in central and peripheral neurotransmission of serotonin have been implicated as a potential factor in depression.[60] Based on these findings, one could hypothesize serotonin's role in genioglossus muscle activity via the hypoglossal nerve, compromising upper airway patency. Though serotonin may play a role in both OSA and depression, the true role of serotonin remains unclear.

**Other explanations.** Obstructive sleep apnea, depression, and cardiovascular disease are associated with elevated levels of various pro-inflammatory substances and cytokines. Some of these markers are implicated in the relationship between depression and coronary artery disease.[61] Interleukin 6 (IL6) and tumor necrosis factor (TNF) are thought to be responsible for increased daytime sleepiness. Administration of a TNF antagonist has been shown to reduce daytime sleepiness. TNF is found to be increased in patients with depression.[62] These pro-inflammatory markers seem to be significant mediators between depression as well as OSA and coronary artery disease. Furthermore, obesity, particularly visceral obesity, is associated with an elevation in these cytokines and could be a feature of depression that would worsen the severity of OSA.

## TREATMENT EFFECTS

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 dilatator muscles, blunt the arousal response to hypoxia and hypercapnia, and increase the arousal threshold for the apneic event, therefore increasing the number and duration of apneas.[63,64]

In a recent study by Habukawa et al,[65] 17 patients with treatment-resistant depression and comorbid OSA completed the BDI, Hamilton Rating Scale for Depression[66] (HRSD), and ESS at the outset and after two months of CPAP treatment. BDI and HRSD scores decreased from 19.7 to 10.8 ($p<0.01$) and 16.7 to 8.0 ($p<0.01$), respectively, after two months of CPAP treatment. Engleman et al[67] showed an improvement in a comprehensive battery of mood and cognitive assessment scales after four weeks of CPAP treatment in 32 patients with moderate OSA[67] as well as in 16 patients with mild OSA.[68] In 2003, Means et al[69] reported improvement on BDI depression scores after three months of treatment in 39 patients with OSA.

In a systematic literature review of 26 studies, nine studies evaluated the impact of CPAP on psychological status. Six of the studies used a comparison group for CPAP treatment other than pretreatment status. Three studies demonstrated, though not conclusively, an overall improvement in psychological performance. Five out of eight studies demonstrated statistically significant improvement in depression, and no studies showed worsening of mood. Thus, McMahon et al[70] asserted that, based on randomized, controlled studies, CPAP has a significant and positive impact not only on subjective sleepiness but also on depression. Other findings of positive effects on fatigue, general health-related quality of life, vigilance, and driving performance were noted when all prospective trials were considered in this review.[70]

Published reports also show negative findings suggesting that the improvement of mood symptoms may not be clearly related to treatment of OSA. One study found no significant difference when comparing subtherapeutic CPAP to mimic placebo effects with effective CPAP treatment.[71] Henke et al[72] also found no significant difference in improvement of depression scores after a short CPAP treatment duration of 1 to 3 weeks. However, they did find positive influence on mood noted in both the treatment and control arms on CPAP. Borak et al[73] found no improvement in emotional status relevant to depression after three and 12 months of CPAP therapy in 20 patients with severe OSA. Similarly Munoz et al[59] found no improvement of BDI scores in 80 subjects with severe OSA after 12 months of CPAP. In these negative studies the CPAP adherence was not monitored.

## CONCLUSION

OSA and depression are common comorbid disorders with serious health consequences. The prevalence of depression is higher in patients with OSA as compared to the general population.

The published literature from 2000 to 2011 is not conclusive due to methodological differences, such as

**TAKE HOME POINTS**

1. Symptoms of obstructive sleep apnea (OSA) and depression overlap and may, therefore, complicate diagnosis and treatment of each disorder.
2. Clinicians should evaluate patients with OSA for depression initially using screening tools, and if positive established criteria should be used to confirm the diagnosis.
3. Effective treatment of both OSA and depression should be considered to improve overall quality of life.

variability of diagnostic tools for depression and OSA. However, studies showing a higher rate of depression in patients with OSA favors a mutual relationship. Also, the treatment effect of CPAP on depression is not conclusive either. Available evidence that treatment of OSA improves depression is limited and cannot distinguish improvement of the depressive disorder *per se* from remitted fatigue and EDS.

An exact pathophysiological relationship between OSA and depression is not fully understood. Further randomized, controlled studies utilizing established diagnostic criteria for OSA and MDD are needed.

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