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REVIEW

Comorbid depression in obstructive sleep apnea: an under-recognized association

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Abstract
Background Obstructive sleep apnea (OSA) and depression may coexist in the same patient. This article aims to review the link between OSA and comorbid depression and critically evaluate the results of studies that assessed the correlation between OSA and depression, the impact of OSA treatment on comorbid depression, and the impact of comorbid depression on continuous positive airway pressure (CPAP) adherence.
Methods An integrative review was conducted on English language studies and reports that assessed the relationship between OSA and depression. Studies were identified by searching PubMed, Web of Science and Google Scholar databases, and reference lists of included studies.
Results Generally, cross-sectional studies show a higher prevalence of depression among OSA patients with both community and sleep disorder clinic samples. Nevertheless, the relationship between OSA and depression is complicated by the fact that the disorders have overlapping symptoms. Longitudinal studies demonstrate an increased risk of developing depression among people with OSA, as well as an association between OSA severity and the likelihood of developing depression. On the other hand, studies assessing the impact of CPAP therapy on depression among OSA patients report conflicting results. Therefore, it is essential to consider how the disorders affect one another and to understand the clinical consequences of treating each disorder in isolation.
Conclusion Depression is prevalent among patients with OSA both in the community and in sleep disorder clinics. Clinicians in general should be aware of this significant association and should aim to treat both disorders.

Keywords Depression · Obstructive sleep apnea · CPAP

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Introduction

Major depressive disorder is characterized by a persistent sad mood or loss of interest in previously pleasurable activities, in addition to affective, cognitive, and neurovegetative changes that have a negative impact on daily functioning [1]. Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, typically in association with arousals, intermittent blood oxygen saturation reductions, and a perception of poor quality sleep. The OSA syndrome includes daytime symptoms, such as poor concentration, fatigue, and excessive daytime

sleepiness (EDS) [2, 3]. Both OSA and depressive disorders are common among adults. Several studies have examined the relationship between depression and OSA, as well as the impact of the treatment of OSA on depression [4–7]. In reviewing this literature, several methodological issues need to be considered, such as the definition and measurement of depression, the methodology used to diagnose OSA, and the proper control for possible confounders (e.g., obesity, gender, age, and OSA comorbidities) [4]. Moreover, most of the depression scales used to assess depression have not been validated in OSA patients. The relationship between OSA and depression is further complicated by the fact that these disorders have overlapping symptoms such as fatigue, poor concentration, loss of interest, insomnia, and decreased libido, and they share common comorbid medical conditions such as obesity, metabolic syndrome (MetS), and systemic inflammation [1, 3, 4, 8, 9]. Although numerous previous studies have investigated the prevalence of depression among OSA patients, the relationship between these two disorders, the effect of OSA therapy on depression, and the impact of comorbid depression on continuous positive airway pressure (CPAP) adherence in OSA patients have received less attention.

Prevalence of depression in patients with OSA

Depression has been diagnosed using clinical questionnaires for mood disorders, clinician assessments, or patients' self-reported symptoms. Studies have assessed the prevalence of depression among OSA patients in clinical settings and in community samples. Questionnaires that have been employed include the Beck Depression Inventory (BDI) [10], the Center for Epidemiological Studies Depression Scale (CES-D) [11], the Minnesota Multiphasic Personality Inventory (MMPI) [12], the Profile of Mood States (POMS), the Hospital Anxiety and Depression Scale (HADS) [13], the Patient Health Questionnaire (PHQ-9) [14], the Hamilton Rating Scale for Depression (HRSD), the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version-Self-Rating Version (SIGH-SAD-SR), the Symptom Checklist 90 (SCL-90) [15], the Mini International Neuropsychiatric Interview 6.0 (MINI) [16], and the Zung Depression Rating Scale (ZDRS) [17]. Among these instruments, only the CES-D and MINI were specifically designed to diagnose depression. The remaining scales are severity-rating instruments intended for use after the clinical diagnosis of depression is established. Even the structured interviews such as CES-D and MINI have their own limitations. For example, they cannot rule out other conditions that may resemble depression, such as chronic fatigue syndrome and fibromyalgia.

Prevalence in community samples

Several large-scale studies assessed the prevalence of depression comorbid with OSA in the general population. In a study conducted in five European countries that included 18,980 adults, Ohayon [18] employed the Sleep-EVAL expert system (based on Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, criteria) through a telephone survey to identify sleep-related and depressive symptoms [18]. Among individuals with a diagnosis of OSA or a DSM-IV breathing-related sleep disorder, the prevalence of DSM-IV major depressive disorder was 17.6 % [18]. The study also revealed that 18 % of individuals with a diagnosis of major depressive disorder met the DSM-IV criteria for breathing-related sleep disorders [18]. This association persisted after controlling for obesity and hypertension [18]. In a large retrospective study of US Veterans Health Administration (VHA) patient records (approximately four million veterans), 118,105 had physician-diagnosed OSA [19]. Among those with OSA, 21.8 % had physician-diagnosed depressive disorder, which was nearly three times the prevalence for patients without OSA [19]. In a US National Health and Nutrition Examination Survey (NHANES) that included 9714 adults, respondents were asked about the frequency of OSA symptoms and completed the 9-item PHQ-9 [20]. Among people with physician-diagnosed OSA, the odds-ratio (OR) for probable major depression was 2.4 among men (95 % CI, 1.5, 3.6) and 5.2 among women (95 % CI, 2.7, 9.9) [20]. In a fourth study that used the Hordaland Health Study data in Norway, Sivertsen et al. [21] studied 7028 working middle-age subjects to assess the association between self-reported OSA symptoms and long-term sick leave and work disability. The depression rating score mean was significantly higher among participants with OSA symptoms. However, all of these studies had cross-sectional designs and therefore were unable to assess the cause and effect relationship between OSA and depression. In addition, the above data raise the question of whether a sub-group of OSA patients has overlapping clinical symptoms resembling depression or if they truly suffer from a mood disorder. These issues are especially important given the new data suggesting that patients with OSA may have different patterns of clinical presentation and different clinical profiles [2].

Prevalence among patients in sleep clinics

Several investigators reported the prevalence of depression among sleep clinic patients diagnosed with OSA. In general, these studies found a relatively high prevalence of depression in patients with OSA (5–63 %) [22]. Schwartz et al. [23] reported a depression prevalence of 50 % using the BDI scale with 50 OSA patients. Yamamoto et al. [24] employed the ZDRS and reported depression in 63 % of 41 severe OSA patients. In a

study conducted with 167 Dutch sleep clinic referrals, Vandeputte and de Weed [25] found that 41 % of OSA patients had a BDI score of ≥10, which indicates probable depression. In a study of 406 OSA patients at a sleep clinic in the USA, Wahner-Roedler et al. [26] reported that 38 % of women and 26 % of men had self-reported depression. Another sleep clinic study showed that self-reported depression was present among 7.9 % of women (n=191) and 6.7 % of men (n=193) diagnosed with OSA [27]. Using the BDI with patients diagnosed with moderate to severe OSA, McCall et al. [28] reported that 28 % of women (n=29) and 6 % of men (n=92) had moderate to severe depression. In an Iranian sleep clinic population of 685 OSA patients, Asghari et al. [29] reported that BDI depressive symptoms were present in 70 % of women versus 49 % of men. A Peruvian study conducted with 244 OSA patients reported that 18 % of patients had BDI-defined depression [30]. In a recent Australian study conducted among patients referred to a sleep clinic due to snoring, 28 % had physician-diagnosed depression and 32 % had HADS scores and 25 % had MINI scores suggesting depression [31].

In contrast to the above studies, some investigators have reported no difference in the prevalence of depression in OSA patients compared with control groups. In a 5-year longitudinal assessment of elderly patients with OSA (n=42), Phillips et al. [32] found no difference in the prevalence of depression between people with and without OSA. In another large-scale study of patients referred to a sleep clinic with suspected OSA (n=2271), the authors found no relationship between OSA and depression, as indicated by the SCL-90 [33]. In a recent study conducted on 671 adult patients with OSA, chart diagnosis of depression was similar in the OSA (40.9 %) and the non-apnea groups (40.3 %) [34].

Few studies have investigated the prevalence of depression among children with OSA. However, a recent meta-analysis included 11 studies that assessed depressive symptoms in children diagnosed with OSA (n=894) and in a comparison group (n=1096) [35]. The authors reported a significant medium relationship between depressive symptoms and OSA among children [35].

In summary, most of the prevalence studies demonstrated significantly higher rates of depression among OSA patients in the general population and in sleep clinic settings. The variations in the reported results and in the prevalence of depression among the studies no doubt partially reflects the differences between the scales and screening instruments used to indicate depression. The variability in the reported rates also can be attributed to confounder effects and comorbidities that were not adequately controlled and to the methodologies employed to diagnose OSA. The studies did not necessarily use comparable severity criteria, and not all of the studies included polysomnographic recordings to confirm the OSA diagnosis.

Correlation studies

The increased prevalence of depression among OSA patients does not imply that depression is necessarily due to the OSA. Depression may be associated with other OSA comorbidities, such as obesity and MetS. To support an etiologic link between OSA and depression, temporal, and dose–response relationships need to be demonstrated.

Cross-sectional study design

In a study that comprised 190 women and 165 men with OSA, there was no relationship between OSA severity as measured by desaturation and depression as measured by the CES-D or by atypical depression items from the SIGH-SAD-SR scale [36]. In an NHANES study (2005–2008) in the USA that included 9714 adults, snoring was not associated with depressive symptoms in men and women [20]. However, snorting/stopping breathing ≥5 nights/week was strongly associated with probable major depression in men (OR=3.1, 95 % CI, 1.8, 5.2) and women (OR=3.0, 95 % CI, 1.6, 5.4) [20]. In another cross-sectional study of 685 recently diagnosed OSA patients, the Apnea-Hypopnea Index (AHI) showed no significant correlation with the BDI score [29]. A small study of 53 OSA patients demonstrated a significant correlation between BDI and Epworth sleepiness scale (ESS) scores (r=0.342, P=0.012) [37]. However, no correlation was found between the BDI scores and OSA respiratory disturbance index (RDI) disease severity [37]. In an observational study of 240 patients with OSA, HADS correlated with the degree of sleepiness (r=0.252, P<0.0001) and inversely with hypoxemia (r=−0.231, P<0.0003) but not with AHI (r=0.116, P>0.05) [31]. In another study that included 49 newly diagnosed untreated OSA patients without major comorbidities, AHI was not correlated with the BDI score [38]. The authors suggested that mechanisms other than the number and frequency of hypoxic events and arousals occurring with apneas contribute to adverse health effects in OSA [38]. Tables 1 and 2 present a summary of the studies that examined the association between depression and OSA. In summary, these studies have demonstrated a positive correlation between EDS and depression. OSA patients who demonstrate EDS also feel tired and fatigued, so this could be one reason why EDS is frequently reflected as depression. However, additional underlying factors related to sleep disruption, intermittent hypoxia, and metabolic, autonomic or inflammatory processes could contribute to the relationship.

Longitudinal study design

Prospective longitudinal studies are also necessary to demonstrate a causal link between OSA and depression. In a large longitudinal study of individuals randomly selected from a

Table 1 A summary of the studies that showed correlation between depression and OSA severity

Author	Study population	Depression assessment tool	OSA diagnosis measures	Conclusion
Enright et al. [39]	5201 participants of a community sample of elderly men and women	CES-D	Self-reported and bed-partner observed apneas	Observed apneas were associated with depression in women, not in men
Smith et al. [40]	Records of 773 patients with OSA and matched controls from the general population	Clinician-diagnosis	Clinician-diagnosis	OSA patients had an OR of 1.4 for depression
Sforza et al. [41]	44 OSA patients and 16 snoring patients clinical setting	HAD-D	PSG	No correlation between HAD-D score and AHI; but positive with oxygen desaturation
Aloia [5]	93 patients with moderate to severe OSA clinical setting	BDI	PSG	Obesity and apnea severity (RDI) differentially contribute to depressive symptoms.
Peppard et al. [7]	1408 participants randomly selected from a working population	Modified Zung Depression Scale or use of an antidepressant	PSG	Moving from one OSA severity level to the next was associated with 1.8-fold increased adjusted odds for the development of depression
Lee et al. [42]	302 male patients with severe OSA	BDI	PSG	RDI is not independently associated with the BDI. A mediational role of subjective sleep quality on the relationship between apnea severity and depressive symptoms in male patients with severe OSA
Wheaton et al. [20]	Interviewed 9714 adults in the community	PHQ-9	Frequency of OSA symptoms	Snoring was not associated with depression symptoms in men and women. However, snorting/stopping breathing ≥5 nights/week was strongly associated with probable major depression in men (OR=3.1) and women (OR=3.0)
Chen et al. [43]	2818 newly diagnosed and untreated OSA patients who were followed for 1 year and 14,090 controls Health Insurance Research Database	Physician diagnosis	PSG	Cox proportional hazards model showed that patients with OSA were independently associated with a 2.18 times increased risk of subsequent depressive disorder within a year, compared to those without OSA

Table 2 A summary of the studies that showed no correlation between depression and OSA severity

Author	Study population	Depression assessment tool	OSA diagnosis measures	Conclusion
Kripke et al. [36]	Community sample of 335 patients	CES-D or items from SIGH-SAD-SR	Desaturation	No relationship
Pillar & Lavie [33]	2271 referrals to a sleep clinic	SCL-90	PSG	Neither the existence nor the severity of SAS was associated with depression
Asghari et al. [29]	685 recently diagnosed OSA patients clinical setting	BDI	PSG	AHI showed no significant correlation with BDI score
Ishman et al. [37]	53 OSA patients clinical setting	BDI	PSG	Significant correlation between BDI and ESS scores. No correlation found between BDI scores and OSA disease severity (RDI)
Douglas et al. [31]	240 patients with OSA clinical setting	HADS	PSG	HADS correlated with the degree of sleepiness and inversely with hypoxemia but not with AHI
Macey et al. [38]	49 newly diagnosed untreated OSA patients without major comorbidities clinical setting	BDI	PSG	AHI was not correlated with BDI score
McCall et al. [28]	121 patients with moderate to severe OSA clinical setting	BDI	PSG	Daytime sleepiness, RDI, number of desaturations, and mean desaturation were not related to BDI
Daabis and Gharraf [44]	72 newly diagnosed OSA patients and 30 controls clinical setting	HADS	PSG	No significant relationship between severity of psychological symptoms and AHI or nocturnal hypoxemia
Rezaeitalab et al. [45]	178 adult OSA patients clinical setting	BDI	PSG	No association between the severity of OSAS and incidence of depression

working population (n=1408), participants were evaluated for OSA by in-laboratory PSG and for depression by the ZDS. Evaluations were performed at 4-year intervals [7]. Moving from one OSA severity level to the next was associated with 1.8-fold increase in the adjusted odds for the development of depression [7]. In adjusted models for age, body mass index (BMI), alcohol, and history of cardiovascular disease (CVD), the odds for developing depression were increased by 2.0-fold in participants with mild OSA and by 2.6 in those with moderate or severe OSA [7]. The 4-year interval data demonstrated an association between OSA severity and the risk of developing depression. In a recent unique longitudinal study conducted in Taiwan that assessed the impact of newly diagnosed and untreated OSA on physician-diagnosed depression, patients (n=2818) were followed for 1 year to identify a subsequent depressive disorder [43]. During the 1-year follow-up, the incidence of depressive disorder per 1000 person–years was approximately twice as high among patients with OSA (18.10, 95 % CI=13.62–23.61), compared with those without OSA (8.23, 95 % CI=6.83–9.84). The Cox proportional hazards model showed that the risk of subsequent depressive disorder within 1 year in patients with OSA increased 2.18 times, compared to those without OSA [43]. The study demonstrated higher risks of depressive disorder among women with OSA. The adjusted hazard of depressive disorder during the 1-year follow-up period among women was 2.72 (95 % CI=1.68–4.40) compared with 1.81 among men (95 % CI=1.09–3.01) [43].

Impact of OSA treatment on depression

If a causal relationship exists between OSA and depression, then depression should be expected to improve with effective OSA therapy. Although randomized clinical trials that have assessed the positive effects of CPAP treatment in OSA patients have demonstrated the benefits of therapy on several symptoms and comorbidities such as daytime sleepiness, quality of life, and blood pressure [46, 47], few studies have explored the effects of CPAP therapy on depression in OSA patients. Most of the observational studies that assessed the effect of CPAP therapy on depression among OSA patients demonstrated a reduction in depressive symptoms [23, 48, 49]. However, a 2006 Cochrane meta-analysis that included data from five clinical trials comparing CPAP with placebo and assessed depression using the HADS scale showed that while the pooled fixed effects significantly favored CPAP, there was no significant effect of CPAP treatment after the application of random effects modeling [50]. A randomized controlled trial that used the Geriatric Depression Scale (GDS) reported no significant difference in the change in depression between the control and CPAP therapy arms [51]. Two subsequent short-term (2 weeks of CPAP therapy) randomized controlled trials reported no mood improvement associated with CPAP [52, 53]. However, most of the above mentioned studies assessed the outcome of depressive symptoms after only 2 to 4 weeks of CPAP use, while the effect of antidepressant treatment in intervention studies typically takes 4–6 weeks or longer before any significant response to treatment is evident [54]. In a more recent study that included 17 patients with treatment resistant depression and comorbid OSA, the investigators assessed the effect of 2 months of CPAP therapy on depression utilizing the BDI and HRSD [55]. CPAP therapy resulted in significant reductions in the BDI (19.7 to 10.8) and HRSD (16.7 to 8.0) scores (both P<0.01) [55]. In a recent multicenter observational longitudinal study that included 300 patients with OSA and depressive symptoms (measured by the 13-item, self-rated Pichot depression scale [QD2A]≥7) at diagnosis and during follow-up for at least 1 year, there was significant improvement in depression scores in response to CPAP therapy [56]. However, 42 % of the patients displayed persistent depressive symptoms after 1 year of CPAP therapy. Multivariate analysis demonstrated that the persistence of depressive symptoms was independently associated with persistent EDS (OR, 2.72), comorbid cardiovascular disease (OR, 1.76), and female sex (OR, 1.53) [56]. The findings of this study are consistent with previous research demonstrating the association between EDS and persistent depression in OSA patients treated with CPAP [55, 57]. With the exception of two studies [23, 48], all the above studies used objective measurements (time meter) to assess CPAP adherence.

Recently, Povitz et al. [54] published a systematic review and meta-analysis evaluating the efficacy of CPAP or mandibular advancement devices (MAD) in treating depression in OSA patients. The authors identified 19 randomized controlled CPAP trials that assessed depressive symptoms and found that despite significant heterogeneity among the individual studies, CPAP treatment resulted in significant improvement in depression compared with control groups (Q statistic, P<0.001; I^2=71.3 %, 95 % CI, 54 %, 82 %). Treatment with a MAD device was also shown to be significantly beneficial for depressive symptoms.

The varied findings regarding CPAP efficacy in improving depression among OSA patients could be related to the duration of the studies, the initial depression severity, or the coexistence of other comorbidities associated with depression in OSA patients. Overall, it seems that depression may persist in some patients despite good adherence with CPAP therapy. Current evidence indicates that OSA patients with persistent daytime sleepiness despite regular CPAP use are at a higher risk for depression persistence. This group of OSA patients should be monitored carefully for symptoms of depression.

Relationship between depression and CPAP adherence

Viewing the relationship between OSA and depression from different perspective, it should be considered that the presence of depression may influence adherence with CPAP therapy in OSA patients. Depression has been shown to be associated with poor compliance to medications across a range of chronic medical conditions [58]. In a questionnaire-based study that assessed self-reported adherence to CPAP therapy in 178 established CPAP users, depression was associated with lower CPAP use [57]. Another study that objectively assessed the adherence of 122 OSA patients to CPAP therapy 1 month after beginning CPAP treatment reported no effect of depression on CPAP adherence [59]. A recent multicenter observational longitudinal study that included 300 patients with OSA and depressive symptoms at diagnosis followed up patients for at least 1 year and assessed CPAP compliance objectively [56]. At the end of the study, the percentage of patients who used CPAP <4 h/night was not different between patients with persistent depressive symptoms and patients without persistent depressive symptoms (23.2 and 18.9 %, respectively) [56]. Two other small studies found no association between CPAP use and depression [60, 61]. In a recent study, the investigators conducted 1 week of home-based auto-PAP titration and monitored adherence objectively on 240 CPAP-naïve OSA patients [62]. Multiple linear regression analysis revealed that depression significantly predicted fewer hours of auto-PAP use [62]. However, most of the previous studies did not control for confounders, such as OSA symptoms (e.g., daytime sleepiness), comorbid conditions of OSA and depression (e.g., insomnia and anxiety), or use and compliance with antidepressant medications which may influence CPAP adherence. Studies have also suggested that race and ethnicity may influence CPAP adherence in OSA patients [63, 64]. Furthermore, mental disorders may interact with ethnicity to influence CPAP acceptance and adherence. Means et al. [65] assessed rates of CPAP adherence in a large sample of African American (AAs) and Caucasian American (CAs) military veterans with and without comorbid mental health disorders and found that mental health disorders (including mood disorders) influence CPAP adherence in AAs but not in CAs. AAs with a mental health diagnosis used CPAP fewer nights per week and for less time per night at 1 month and for less time per night at 3 months compared with AAs without mental health disorders [65]. Future studies should examine the effect of treatment of depression on CPAP acceptance and adherence and should control for possible confounders that may interact with depression and influence CPAP adherence.

Why OSA and depression coexist

The mechanisms underlying the association between OSA and depressive symptoms are not known. However, a few plausible mechanisms have been proposed [43]. Poor sleep quality and frequent arousals during sleep in OSA patients may affect mood. Moreover, intermittent hypoxemia that accompanies OSA has been proposed to influence mood. In a randomized controlled trial of OSA patients with comorbid depression, both CPAP and oxygen supplementation resulted in decreased psychological symptoms suggesting that hypoxemia may play a role in the development of depression among OSA patients [53]. On the other hand, OSA is associated with the release of several pro-inflammatory cytokines such as IL-6 and tumor necrosis factor [66]. A similar immune response involving pro-inflammatory cytokines such as IL-1, IL-6, and interferons was noted among patients with depression [67]. Moreover, a few inhibitory and excitatory neurotransmitters, such as serotonin, norepinephrine, and γ-aminobutyric acid (GABA), are involved in both the sleep/wake cycle and mood regulation. Finally, other comorbid chronic conditions such as obesity, diabetes, and cardiovascular diseases are potential causes of depression as depression is prevalent among patients with chronic medical diseases [68].

Conclusion

In summary, depression is prevalent among patients with OSA both in the community and in sleep disorder clinics. Clinicians in general should be aware of this significant association and should aim to treat both disorders. Simple and practical screening tools for depression in sleep disorder clinics should be developed and validated to facilitate the evaluation of depression among patients with OSA. Patients with persistent EDS despite regular CPAP use for OSA should be assessed for depression. Further, large-scale studies are needed to establish the cause and effect relationship between OSA and depression while controlling for possible confounders. Moreover, it is important to evaluate the effect of treatment of depression with antidepressants on CPAP adherence in OSA patients.

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Comments

The review article by BaHamman et al. provides clinicians with an up-to-date summary on the topic of comorbid depression and obstructive sleep apnea; yet, in the 25 years since this comorbidity was described by Millman et al., it remains an "under-recognized association." Obstructive sleep apnea likely remains under-recognized by behavioral health providers, and depression is typically not screened for in sleep disorders centers. As the authors

note, much of the research utilizes screening tools and questionnaires that are intended for rating severity, and potentially tracking symptoms and response to therapy, rather than diagnosing depression.

Patients with depression who fail to respond to treatment should absolutely be screened for obstructive sleep apnea. By the same token, screening for depression should occur in OSA patients with unexplained poor PAP adherence or excessive daytime sleepiness despite adequate adherence. Notably, depression can negatively impact PAP compliance, just as occurs with compliance for numerous other medical comorbidities. While recent studies have shown modest benefits in mood symptoms, and many patients with good CPAP adherence improve, a substantial number will have refractory symptoms of depression despite good adherence. The article by BaHamman et al. highlights the significant gaps in our understanding of these associated illnesses and should serve as a call for clinicians and researchers to increase awareness, improve diagnostic strategies, devise therapeutic regimens, and explain the biologic underpinnings for comorbid depression and OSA.

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