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ORIGINAL ARTICLE

Depression and obstructive sleep apnea

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Abstract

OBJECTIVE: Obstructive sleep apnea (OSA), is described as intermittent interruptions or reductions in airflow which are initiated by an incomplete or complete collapse of the upper airways despite respiratory effort. When left untreated, OSA is connected with comorbid conditions, such as cardiovascular and metabolic illnesses.

METHOD: The PubMed database was used to examine papers published until April 2017 using the subsequent terms: „obstructive sleep apnea" or "obstructive sleep apnoea" and "depression" in successive combination with "CPAP (continuous positive airway pressure)", "therapy", "pharmacotherapy", "psychotherapy", "cognitive behavioral therapy" or "quality of life".

RESULTS: After assessment for the suitability, 126 articles were chosen. The numerous evidence of a connection between OSA and depressive symptoms, as well as depressive disorder, were found. This connection may be directly or indirectly linked due to the participation of some OSA mediators consequences such as obesity, hypertension, and the decreased quality of life. Patients with the comorbid major depression and OSA reported more severe and longer episodes of depression. Nevertheless, the information on the effect of the treatment of OSA using CPAP on the depressive symptoms was limited. Still, the current state of the art suggests that this treatment decreases the severity of the comorbid depressive symptoms.

CONCLUSIONS: It is important to evaluate the symptoms of depression in the patients with OSA. On the other side, a psychiatrist should not just treat the depression, as it is also important to screen individuals at high risk of OSA when assessing patients for depressive disorder, especially those with depression resistant to treatment.

INTRODUCTION

The links between depression and sleep breathing disorders have been discussed profoundly in the past. For thousands of years, people have seen a reciprocal link between emotional health and sleep. For example, stress, anxiety, and depression have all been found in discussions about sleep in ancient religious texts (Ancoli-Israel 2001). Many sleep difficulties have been believed to impact the emotional wellbeing adversely. At present, one of frequently discussed sleep breathing disorders is obstructive sleep apnea (OSA).

OSA is characterized by recurrent cessations or decrease of the air flow (apneas and hypopneas) during sleep, complemented by oxygen desaturation and arousals (Punjabi 2008). The disorder is linked to increased morbidity and mortality and reduced quality of life (Pelletier-Fleury *et al.* 2004; Peppard *et al.* 2006; Somers *et al.* 2008). Multiple studies have found that age, sex, obesity, pharyngeal anatomic abnormalities, snoring, and cephalometric features could be risk factors for OSA in the general population (Dixon *et al.* 2003; Kubota *et al.* 2005; Rodsutti *et al.* 2004). The prevalence of OSA, which depends on definition and method of its evaluation, is estimated at 2 to 14% in middle-aged adults (39–59 years). However, it shows a rise to 20% in individuals older than 60 years (Eikermann *et al.* 2007). The significant epidemiological investigation using polysomnography in-home in the US found that the OSA prevalence, defined by AHI >15 was 18% in the general population (Young *et al.* 2008).

Several mechanisms are leading to airflow restriction, intermittent hypoxia, and arousals from sleep in OSA (Eckert & Malhotra 2004). The sleep breaking up is one of the most important reasons of excessive sleepiness in daytime, the principal clinical manifestation of OSA. Hypoxemia/hypercapnia, sleep fragmentation as well as excessive oscillations in the the intrathoracic pressure, heart rhythm, and the blood pressure, are the most significant acute functional consequences of untreated OSA (Somers *et al.* 2008; Sova *et al.* 2015). The long-term complications of the OSA are cardiovascular disorders, mainly hypertension, and rise cardiovascular risk of the stroke (Shamsuzzaman *et al.* 2003; Sonka *et al.* 2007; Peppard *et al.* 2013), decreased the perception of high-frequency sound (Vorlova *et al.* 2016), worsening of cognitive functions (Kim *et al.* 1997; Yaffe *et al.* 2011; Canessa *et al.* 2011; Torelli *et al.* 2011), and premature death (Young *et al.* 2008). In the field of psychiatry, OSA is associated with depression (Vandeputte & Weerd 2003; Peppard *et al.* 2006), poor quality of sleep, poor memory and irritability (Ferini-Strambi *et al.* 2003; Fleetham *et al.* 2006; Harris *et al.* 2009), and decreased the quality of life (Baldwin *et al.* 2001; Peppard *et al.* 2006).

As for the emotional health, the interrupted sleep pattern affects the stress system of the body and thus makes those suffering from OSA more vulnerable to depression (Meerlo *et al.* 2008). Therefore, the treatment of the patients with OSA has to be complex and multidisciplinary. The aim of this review is to determine how OSA affects depressive symptoms and how significant is a relation between OSA and depression.

One of the reasons why it is important to address this topic is poor compliance to the treatment of CPAP (continuous positive airway pressure) of patients with depression symptoms. CPAP is a device that generates positive airway pressure, which is delivered via a hose to a nasal (or full-face) mask. From their ranks will more often recruit patients, who cannot tolerate the CPAP mask in the night and subsequently do not use it. Lower tolerance is often by those who suffer anxiety or claustrophobia. Another reason that is mentioned above is a cross-disciplinary collaboration, where the psychiatrist may, in recognition of the typical patterns, send the patient to the Sleep Laboratory to the treatment with CPAP. Moreover, on the contrary, a pulmonary specialist in Sleep laboratory can give more attention to OSA patients with depression and ask psychiatric consultation for help.

METHOD

The PubMed database was used to search for papers published from January 1953 to April 2017 using the following keywords: „obstructive sleep apnea“ or "obstructive sleep apnoea"and "depression" in successive combination with "CPAP," "therapy", "pharmacotherapy," "psychotherapy," "cognitive behavioral therapy", or"quality of life." Additionally, the selected papers had to meet these criteria for inclusion: (1) published in peer-reviewed journals; (2) studies in humans; or (3) reviews on the related topic; (4) accessible in English. The criteria for exclusion were: (1) abstracts from conferences; (2) commentaries; (3) subjects younger than 18 years.

The total of 514 articles was nominated by primary assortment using keywords in different combinations. After the selection according to the including and excluding criteria, 80 articles were chosen. After a complete inspection of the full texts, 57 papers have been selected. Secondary papers from the reference lists of the primarily designated papers were searched, assessed for the suitability, and added to the first list of the papers (n=69). This way, 126 papers were included in the review process (Figure 1), as recommended by the PRISMA Guidelines (Moher *et al.* 2009).

RESULTS

Symptoms of depression in patients with OSA

The evidence of the linkage between depression and OSA is various. Some authors published that patients with OSA do not exhibit a clinically significant degree of depression, or have levels of depressive symptoms no higher than healthy controls (Lee 1990; Gall &

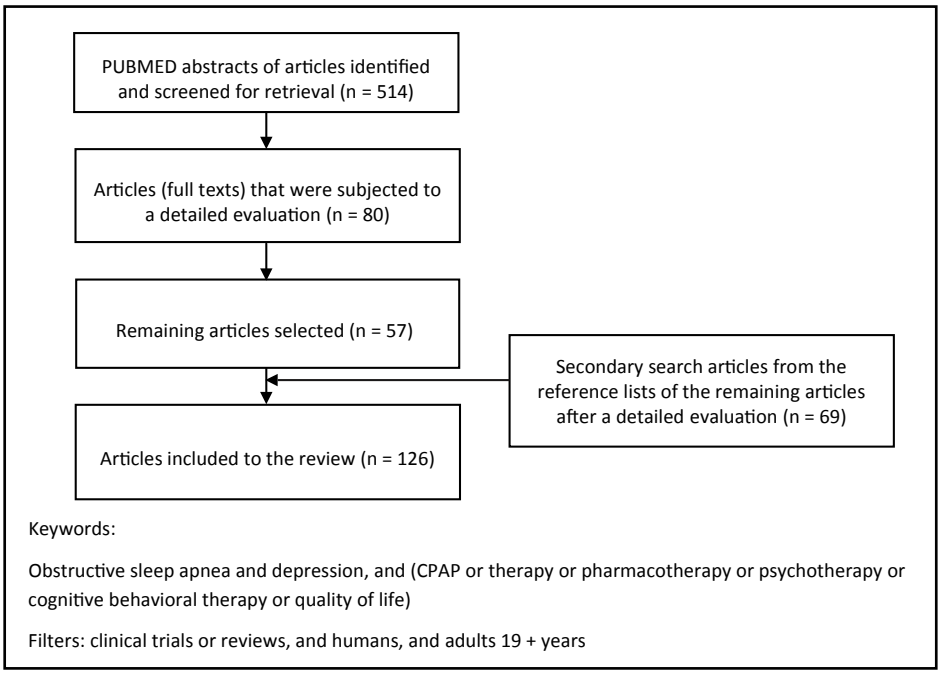

Fig. 1. Summary of the selection process.

Isaac 1993; Flemons *et al.* 1994) or patients with other chronic illnesses (Klonoff *et al.* 1987). In an investigation of 60 patients with OSA Lee (1990) showed that none of them met the diagnostic criteria for depression. In another investigation observing 112 OSA patients, the severity of depression was correlated with age, body mass index, and sleep parameters (Bardwell *et al.* 1999). Nevertheless, the severity of OSA was not linked to the seriousness of the depression score. Similar outcomes were found in the study on 2271 patients examined for sleep-disordered breathing (Pillar & Lavie 1998). In this group, the existence of OSA was not connected with depression and anxiety (Pillar & Lavie 1998).

On the other hand, many specialists have found that OSA may be associated with clinically significant depression (Guilleminault *et al.* 1977; Reynolds *et al.* 1984; Millman *et al.* 1989; Cheshire *et al.* 1992; Peppard *et al.* 2006) or an increased level of depressive symptoms (Kales *et al.* 1985; Derderian *et al.* 1988; Platon & Sierra 1992; Borak *et al.* 1994; Edinger *et al.* 1994; Engleman *et al.* 1994; Flemons & Tsai 1997; Ong *et al.* 2009; Senaratna *et al.* 2016). That could be explained either as a straight consequence of the sleep fragmentation or secondarily as a result of the social effects of this illness. Additionally, the level of depression was higher when the sleep apnea syndrome and the nocturnal hypoxemia was more severe (Aikens & Mendelson 1999). Interestingly, Ong *et al.* (2009) study showed that 39% of 51 patients with insomnia and depression also met the OSA criteria.

The essential question is if the occurrence of depressive symptoms is connected with the OSA itself, or it is the consequence of additional features such as drowsiness and decreased health status associated with the apnea and the sleep fragmentation (McNamara *et al.* 1993; Smith & Shneerson 1995). It is mostly believed that OSA triggers depression in some individuals, yet it is unidentified whether this depression is a primary clinical phenomenon or just a secondary consequence of the overlapping somatic symptoms shared by both disorders (Means *et al.* 2003). Also, the decreased quality of life present in OSA patients can disturb their general health perception and emotional well-being and trigger depression (Cassel 1993; Smith & Shneerson 1995). Some of the symptoms frequently reported by the patients with OSA, such as low energy, loss of interest, poor concentration, decreased libido, and cognitive deficiency may correspond with those described in depressive patients and are reliant on a daytime sleepiness (Aloia *et al.* 2005). For this reason, the assessment of the connection between depression and OSA can be quite difficult because it is hard to distinguish the effects of OSA and symptoms of depression that may be similar in some cases. Accordingly, one possible explanation for the high scores of depression in the patients suffering from OSA is that they may often endorse such items on questionnaires of depression. Rather than being related to a depressive disorder, in opposition, affirmative answers may more correctly reflect the costs of the apnea severity. Certainly, this view that depression could be an epiphenomenon of OSA has led some to conclude that the relationship should be hypothesized as a mood disorder secondary to a medical condition (Reynolds *et al.* 1984). Possible proofs for this hypothesis come mainly from studies showing reduced depression following the CPAP treatment (Millma *et al.* 1989; Borak *et al.* 1994; Sánchez *et al.* 2001; McMahon *et al.* 2003), even when the adherence to the treatment is poor (Means *et al.* 2003).

The different indirect view to the association between OSA and depression is mediated by an OSA correlate, such as obesity and insomnia. Figure 2 shows a simplified diagram of possible links between depression, sleep apnoea, obesity, and insomnia. Robust and well-known relations are symbolized by black arrows, weaker and questionable relations are represented by white arrows. Obesity is one or the most important risk factors for the OSA (Kripke *et al.* 1997; Wilhoit & Suratt 1987). In the patients with morbid obesity (BMI more than 40 kg/m^2), the rates of OSA range from 69 to

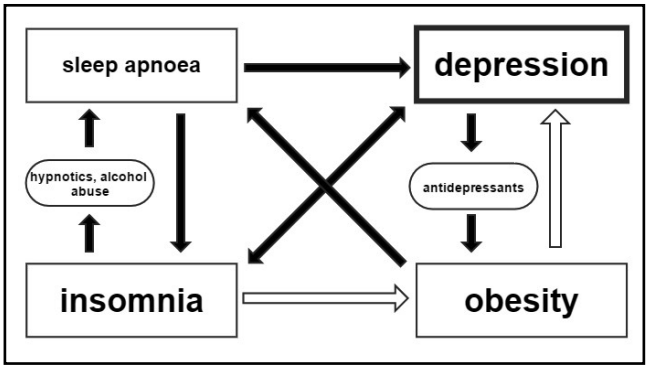

Fig. 2. A simplified diagram of possible links between depression, sleep apnea, insomnia, and obesity – the description in the text.

98% (Valencia-Flores *et al.* 2000; Stanchina *et al.* 2004). Peppard *et al.* (2000) study displayed that a 10% body weight growth increased the relative risk of developing OSA six-fold. Moreover, several studies have published an increased prevalence of depression among obese subjects even without consideration for the presence of OSA (Black *et al.* 1992; Goldstein *et al.* 1996; Carpenter *et al.* 2000). One theory suggests that obese persons suffer from body image dissatisfaction, discrimination, guilt from past failures to lose weight, and psychosocial distress (Wooley & Garner 1991). Additionally, dissatisfaction with the body image was displayed to partially mediate the relationship between depression and obesity (Friedman *et al.* 2002; Sarwer *et al.* 1998). Experimental investigations also support this understanding, presenting that changes in the body image accompanying by significant weight loss are linked with significant decreases in the depressed mood (Dixon *et al.* 2003). These investigations suggest that the obese patients may endorse a different, more cognitive, characteristic of depression than the more fatigue-related, physical characteristic that is likely associated with sleep problems. Furthermore, the antidepressant medication is often accompanied by weight gain and thus worsening of sleep apnoea syndrome.

Repetitive apnoea causes arousal and leads to sleep disturbance and insomnia. The patients with insomnia use and abuse hypnotics and alcohol. Alcohol consumption and use of hypnotics worsen OSA as well. There is also a bidirectional link between insomnia and depression (Khazaie *et al.* 2017). According to some studies, there is also a relation between insomnia and obesity (Crönlein 2016; Moreno-Vecino *et al.* 2017).

There is a robust evidence about the chronic inflammation in OSA, but the exact mechanisms leading to oxidative burst and resulting inflammatory cascade are unclear. The repetitive hypoxia and reoxygenation in patients with OSA may result in the generation of the reactive oxygen species (ROS). These probably play the key role in inflammatory response activation – they activate multiple proinflammatory cytokines – e.g. tumor necrosis factor, inter-leukin-6 (IL-6) and IL-8 via transcription factor nuclear factor-κB (NF-κB), and activator protein. C-reactive protein is profoundly studied biomarker of inflammation; it is produced in response to IL-6. Many studies have confirmed the association between OSA severity and CRP level and a decrease in CRP level after CPAP treatment (Sharma *et al.* 2008; Guven *et al.* 2012; Arter *et al.* 2004). Similarly, there was repeatedly confirmed the decrease in TNF-α and IL-6 after CPAP treatment (Wang *et al.* 2015; Lin *et al.* 2016). Interestingly, elevated levels of proinflammatory markers have also been found in obesity (Lamonaca *et al.* 2017; Zand *et al.* 2017), depression (Liu *et al.* 2012; Al-Hakeim *et al.* 2015), and insomnia (Irwin *et al.* 2015; Devine & Wolf 2016). Therefore, the connection between these disorders is not only the presence of common risk factors but also the chronic inflammation.

Risk factors for depressive disorders comorbid with OSA

Szaulińska *et al.* (2015) referred that OSA is comorbid in 11%–18% of patients with major depressive disorder, 15%–48% of schizophrenic patients, and 21%–43% of patients with bipolar affective disorder, nevertheless in only 5% of the general population (Young *et al.* 2002). Cai *et al.* (2017) explored clinical risk factors predicting OSA in the patients with depressive disorder. They suggested that the rate of depression comorbid with OSA is unusually high and there is a high incidence of unrecognized OSA among the patients with depressive disorder. Hattori *et al.* (2009) examined 32 patients with mood disorder and found that common OSA risk factors (such as snoring, apnea, and body mass index) may help to identify OSA among these patients.

Comorbidity of OSA with major depressive disorder

Studies of prevalence have presented high rates of depression among the OSA patients in both clinical and community population, ranging from 7 to 63% (Schröder *et al.* 2005; Saunamäki & Jehkonen 2007; Harris *et al.* 2009). Additionally, several studies have presented that the patients with OSA and perceive the high severity of depression, a decreased quality of life, and suffer most from daytime drowsiness and a lack of energy (Akashiba *et al.* 2002; Sforza *et al.* 2002; Asghari *et al.* 2012). It has also been presented that in comorbid patients with OSA and depression, daytime sleepiness is more strongly associated with severity of depression than to OSA (Sforza *et al.* 2002; Asghari *et al.* 2012, Kjelsberg *et al.* 2005). Daytime sleepiness has also been presented to be more related to depression than other OSA symptoms in a general population (Bixler *et al.* 2005). Additionally to daytime sleepiness and fatigue, a high comorbidity of insomnia among the patients with OSA reported in previous studies (Björnsdóttir *et al.* 2002, Björnsdóttir *et al.* 2013) could also partly clarify higher levels of depression among this population, as epidemiological studies have indicated that patients with insomnia have nearly four times higher possibil-

ity for the development of a depressive disorder (Selenberger & Soldatos 2005).

Older studies of OSA and psychiatric morbidity had concentrated to the degree of depression in the OSA population. Indicators such as fatigue, loss of interest, decreased libido, and poor concentration shares both depression and OSA, which means that frequently used depression questionnaires may not be suitable for evaluation of the depressive symptoms among the patients with OSA (Harris *et al.* 2009). Overlapping symptoms can also add confusion to clinical diagnosis of both OSA and depression. Most standardized self-report questionnaires used to assess depression among patients with OSA have not been designed for the assessment of this specific population and may, therefore, have problems with their application in patients with OSA. As a consequence, it is unclear if OSA and depression express a real comorbidity or only share similar symptoms (Andrews & Oei 2004; Baran & Richert 2003).

Efforts to overcome the trouble of assessing depressive symptoms where OSA is likely to produce similar symptoms range from study-specific modifications to existing scales (Peppard *et al.* 2006), and they lead to suggestions that only cognitive features of depression, such as self-blame ruminative thoughts, feelings of guilt or worthlessness, and crying, should be used in OSA (Hashmi *et al.* 2006).

Even though depression seems to play a significant role in the overall expression of OSA, the actual nature of this relationship remains undiscovered. The study of Farney *et al.* (2004) has shown that individuals diagnosed with OSA are at higher risk of depression. More current studies report that depression as a disorder may be highly prevalent in patients with OSA, with some surveys reporting that up to 63% of individuals are affected (Harris *et al.* 2009). Epidemiological findings vary according to age, sex and apnea severity. OSA may cause depression on the base of sleep loss, sleep interruption, and cognitive alterations induced by recurrent hypoxemia, while weight gain and sleep disruption due to depression could worsen OSA (Harris *et al.* 2009). Furthermore, the symptoms of OSA might imitate the symptoms of depression, including overall low energy, sleep disruption, reduced will and decision capacity, cognitive deficiency, and a lower quality of life (Szaulińska *et al.* 2015).

Consequences of comorbidity of OSA with major depressive disorder

OSA might exacerbate symptom severity in major depressive disorder (Harris *et al.* 2009). Patients with comorbidity of major depression and OSA reported more severe and longer episodes of depression (Schröder & O'Hara 2005).

Some investigations tried to quantify the power of the relations between excessive sleepiness, OSA, and depression. These investigations suggested that depression, rather than OSA, may be more strongly related with excessive drowsiness (Bixler *et al.* 2005).

Treatment with CPAP and depressive symptoms in OSA using CPAP

Many researchers have concentrated on understanding whether the CPAP treatment improves the depressive states of the OSA patients. CPAP recovers overall OSA symptoms by keeping the upper airways open using the air pressure, which results in a decrease of hypoxemia and sleep fragmentation (Loredo *et al.* 1999; Sovova *et al.* 2012, Calik 2016). According the review and meta-analysis the treatment using CPAP is effective for all grades of OSA (Giles *et al.* 2006; Calik 2016), and has been shown to decrease excessive sleepiness as well as adversative events linked to other medical conditions (Marin *et al.* 2005; Marin *et al.* 2010; Martínez-Garci *et al.* 2009; Hobzová *et al.* 2016). The CPAP treatment increases subjective daytime functioning and performance in cognitive tests (Naegele *et al.* 1998; Bedard *et al.* 1993; Montserrat *et al.* 2001; Muňoz *et al.* 2000; Bardwell *et al.* 2001; Ferini-Strambi *et al.* 2003; Lau *et al.* 2010). However, it remains controversial whether CPAP treatment also recovers depressive symptoms. The results were contradictory for a long time (Borak *et al.* 1996; Yu *et al.* 1999; Muñoz *et al.* 2000; Sánchez *et al.* 2001; Profant *et al.* 2003; Giles *et al.* 2006; Calik 2016; Argun Baris *et al.* 2016). Kerner *et al.* (2015) published that the cognitive performance of the patients with OSA comorbid with major depressive disorder is even worse than that of OSA alone, while some reports advocate that depressive symptoms might be better in at least some patients receiving continuous positive airway pressure therapy or other treatment for OSA (Sánchez *et al.* 2001; Means *et al.* 2003; Schwartz *et al.* 2005; Kawahara *et al.* 2005).

The effect of the treatment of sleep apnea on depressive symptoms has been evaluated in some investigations; however, outcomes have been ambiguous (Giles *et al.* 2006). According to some of them, depression improves after a few months of the CPAP use (Sanchez *et al.* 2001). However, there are also some studies with contradictory results (Muňoz *et al.* 2000). The Giles *et al.* (2006) review concluded that the effects of the OSA treatment on the depressive symptoms were limited and inconsistent between investigations because of a high level of heterogeneity. Povitz *et al.* (2014) performed a systematic review and meta-analysis of randomized controlled trials that examined the effect of CPAP on depressive symptoms in the patients with OSA. In a random effects meta-analysis of 19 studies, the CPAP treatment led to a decrease in depressive symptoms compared to controls, but with significant heterogeneity between the evaluated trials.

The issue of reversibility of depressive symptoms in OSA is dedicated to a wide range of studies (reviews: Giles *et al.* 2006; Povitz *et al.* 2014). Most of them used for the evaluation of the level of depression also BDI-II. Daniel *et al.* (2005) conducted a study with 50 patients, which showed that the percentage of diagnosed depression in the patients with OSA is

significantly higher than in the general population. A month of the CPAP treatment leads to a significant improvement in the depressive symptoms reported in the BDI-II. This is by our results (Hobzova *et al.* 2017). In comparison with this study, however, only 3 of our patients (i.e. 6.7%) were treated with antidepressants. In Daniel *et al.* (2005) study there were 19% of patients on antidepressants. It is also in agreement with the study of Iacono Isidoro *et al.* (2016) which gives evidence that short-term application of CPAP can lead to a general increase in perceived well-being. The improvement in BDI-II after the first month of the treatment was highly significant. Part of the improvement is likely attributable to the fact that some items in the BDI-II inventory non-specifically describe not only the symptoms of depression but also the symptoms of sleep apnea (fatigue, loss of energy, concentration difficulties, changes in sleep). However, the patients mostly showed improvement also in other areas, such as a sense of worthlessness, irritability, sadness, pessimism, disgust with themselves, and loss of pleasure. After the treatment, there was a shift in all areas, which can be explained mainly by enhancing the quality and quantity of sleep that brings relaxation and gives the possibility of regeneration. The patients also reported an improvement in partnership and sexual life and better performance in the job.

Treatment of comorbidity of OSA and depression using antidepressants

OSA might affect response to a pharmacological treatment of depression as well as reduce adherence to antidepressant treatment (Harris *et al.* 2009; Waterman *et al.* 2015). Waterman *et al.* (2015) studied 400 patients with major depressive disorder and recognized that those with comorbid OSA and depressive disorder were 1.5 times less probable to answer to 12 weeks of treatment with the venlafaxine than those with a depressive disorder occurring alone.

Both tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitor (SSRI) antidepressants may decrease sleep efficiency in the OSA patients (Smith *et al.* 2006). Simultaneous use of antihypertensive medications and antidepressants increases the likelihood of a diagnosis of the obstructive sleep apnea syndrome (Farney *et al.* 2004).

Comorbidity with depression has been found to affect treatment adherence, self-management, and functioning adversely and to intensification perception of the symptoms and increase the costs of the treatment of other medical illnesses (Katon 2003; Evans *et al.* 2005). Patient affected by OSA and the depression at the same time, also seem worse off than the patients with OSA only. OSA patients with high severity of depression are individuals with the greatest sleepiness (Kjelsberg *et al.* 2005), and fatigue (Bardwell *et al.* 2007) during the day, and lowest quality of life (Akashiba *et al.* 2003). Information is inconsistent on compliance with the CPAP treatment. In a study of 54 patients with OSA, pre-CPAP depression scores and a post-CPAP improvement were not related to the use of CPAP (Wells *et al.* 2007). However, in a study of 178 patients, depression was related to low compliance with CPAP (Kjelsberg *et al.* 2005).

CONCLUSION

Depression is frequently described as one of the daytime sequelae of OSA, and many studies have found increased rates of depression among the OSA patients. The results of this review advise that mental health practitioners should consider the presence of OSA in patients with depressive symptoms and sleep breathing (disorders) disturbances particularly in individuals with hypertension, with arrhythmias, in male patients (female patients after menopause), patients with higher BMI and in older patients. Physicians should also think carefully about screening for OSA when assessing depressive patients because comorbid OSA may lead to more difficulties to the treatment of depression (Harris *et al.* 2009; Kawahara *et al.* 2005). Specific attention should be paid to the patients with a depressive disorder, who are resistant to the treatment, and psychiatrists should consider an OSA screening. Handling of OSA could improve not only the compliance to the antidepressant treatment but also the treatment response rate for depression (Waterman *et al.* 2015). Psychiatrists involved in treating mood disorders comorbid with OSA should be cautious in using drugs with a muscle relaxant effect such as benzodiazepines. The patients need to balance the benefits and risks of the existing treatments for OSA.

Conflict of Interest

The authors declare no conflict of interest.

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