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ORIGINAL ARTICLE

Obstruction sleep apnoea and panic disorder.

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Abstract

OBJECTIVE: Both panic disorder (PD) and obstructive sleep apnea (OSA) are frequent conditions that can be comorbid. This article reviews the current state of knowledge about the comorbidity of PD and OSA and the effectiveness of therapy in patients with this comorbidity.
METHOD: Articles obtained via PubMed and Web of Science search were selected; the publishing date was between January 1990 and December 2022. The applied search terms were: obstructive sleep apnea; panic disorder; CPAP; antidepressants; anxiolytics; antipsychotics. Eighty-one articles were chosen by primary search via keywords. After a complete assessment of the full texts, 60 papers were chosen. Secondary papers from the references of the primary documents were investigated, evaluated for suitability, and included in the list of documents (n = 18). Thus, seventy-eight papers were incorporated into the review article.
RESULTS: Studies describe a greater prevalence of panic disorder in OSA patients. So far, there is no data on the prevalence of OSA in PD patients. Limited evidence is found regarding the influence of CPAP treatment on PD, and this evidence suggests that CPAP can partially alleviate PD symptoms. Medication used in PD treatment can significantly impact comorbid OSA, as explored in several studies.
CONCLUSIONS: The relationship between the two conditions seems bidirectional, and it is necessary to assess OSA patients for comorbid panic disorder and vice versa. Both disorders can worsen the other and must be treated with a complex approach to ensure improvement in patients' physical health and psychological well-being.

INTRODUCTION

Both panic disorder (PD) and obstructive sleep apnea (OSA) are frequent conditions that often coexist (Yue *et al.* 2003, Thorpy & Plazzi 2011). Panic disorder (PD) is defined by recurring episodes of severe anxiety and the fear of dying, losing one's mind, or losing control with a typical vegetative accompaniment. The somatic symptoms of PD manifest predominantly symptoms from activation of the sympathetic system, such as palpitations, perspiration, chest tightness, and vertigo (APA 2013). A panic attack arises suddenly without associations to any specific situation, and the perceived randomness of the attacks leads to anticipatory anxiety. Panic disorder is connected with agoraphobia in some patients. The lifetime prevalence of isolated panic attacks is 23 to 33.7%, while the prevalence of PD is between 1.5 and 5.1% in the general population (Katerndahl & Realini 1993, Grant *et al.* 2006, Kessler *et al.* 2012, Bandelow & Micheaelis 2015, Auerbach *et al.* 2018). The prevalence of PD is 16% in patients with morbid obesity (BMI – above 40) (Barbuti *et al.* 2022).

Obstructive sleep apnoea syndrome (OSA) is defined by repetitive upper airway collapse during sleep with consequential daytime symptoms (ICSD-3) (Sateia 2014). OSA prevalence is estimated at 2–4% and can lead to excessive daytime sleepiness (Young *et al.* 1993, Kapuer *et al.* 2005, Faber *et al.* 2019). Metabolic and cardiovascular complications, chronic insomnia, and mood disorders could be consequences of OSA (Amdo *et al.* 2016).

Both disorders are frequent in the general population and are often comorbid (Sharafkhaneh *et al.* 2005, Barbuti *et al.* 2014). Also, respiratory events during sleep in OSA may trigger nocturnal panic attacks (Stein *et al.* 1995). A large cohort study by Sharafkhaneh *et al.* (2005) showed that the prevalence of anxiety in patients with OSA was approximately two times more than in the general population. Moreover, panic disorder and OSA have known risk factors for cardiovascular complications, which may raise mortality (Marin *et al.* 2005). For this reason, carefully managing individuals with both conditions is vital in preventing cardiovascular morbidity and mortality (Smoller *et al.* 2007).

Continuous positive airway pressure (CPAP) is an intervention that prevents upper airway collapse throughout sleep and is a first-line treatment for OSA (ATS 1994). CPAP therapy can help with cardiovascular morbidity in OSA, reducing mortality and depressive symptoms induced by OSA (Marin *et al.* 2005, Schwartz *et al.* 2005, Hobzova *et al.* 2017, Vanek *et al.* 2020). Regarding panic disorder, CPAP therapy has been reported in a few case studies to achieve a substantial decrease or remission of panic disorder symptoms in individuals with panic disorder and OSA (Enns *et al.* 1995, Trajanovic *et al.* 2005). However, systematic evidence of the efficiency of CPAP intervention on panic disorder was assessed only in an open trial and one randomized cross-sectional study on the efficacy of CPAP in panic disorder symptoms in individuals with OSA (Edlund *et al.* 1991, Takaesu *et al.* 2012).

This narrative review summarizes the current knowledge on the comorbidity of panic disorder and OSA and the effectiveness of CPAP on comorbid PD with OSAS.

METHOD

Articles were obtained via PubMed and Web of Science search. The date of publishing was set for the period between January 1990 and December 2022. The authors conducted a sequence of literature investigations with various keywords: obstructive sleep apnea, panic disorder; CPAP; antidepressants; anxiolytics; antipsychotics. The papers were chosen according to the following inclusion criteria: (1) published in peer-reviewed journals; (2) studies in humans; or (3) reviews on the related topic; (4) English language. The exclusion criteria were: (1) commentaries and (2) subjects younger than 18. Additional articles were used from the references of originally selected articles. Eighty-one articles were chosen in the primary collection using keywords. After the application of inclusion and exclusion criteria, 68 papers were included. After the assessment of the full texts, 60 papers were chosen. Secondary papers from the references the selected papers were investigated, evaluated for suitability, and integrated into the list of articles (n = 18). Seventy-eight papers were integrated into the review (Figure 1).

RESULTS

Comorbidity of panic disorder and obstructive sleep apnoea

Prevalence of panic disorder in OSA patients

A study of nocturnal sleep deprivation in subjects with PD showed a worsening of anxiety and panic episodes in 40% of subjects the following day (Roy-Byrne *et al.* 1986). Furthermore, the level of anxiety and depression symptoms was associated more with sleep deficiency and subsequent daytime tiredness than with nighttime hypoxia or AHI (apnea-hypopnea index) in patients with OSA (Yue *et al.* 2003). Another study pointed out that panic attacks during sleep worsen overall outcomes via insomnia in patients with this comorbidity (Thorpy & Plazzi 2011). Appleton *et al.* (2016) described an independent link between OSA and anxiety spectrum disorders. Other authors think about the connection between OSA and mental disorders, which is reflected, for example, in efforts to standardize questionnaires for anxious and depressive signs in patients with OSA or screening for psychiatric disorders in patients with disturbed sleep (Law *et al.* 2014). One study described a present mental disorder in 22% of OSA patients – 3% of patients had panic disorder, and 12% suffered from

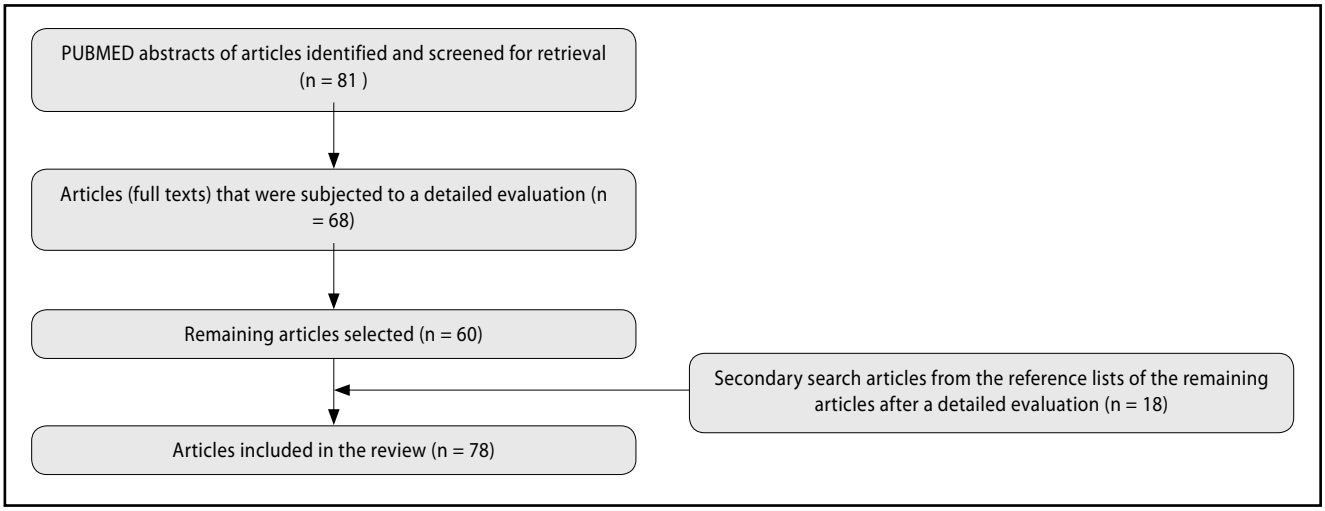

Fig. 1. Summary of the selection process
Keywords: Obstructive sleep apnea and panic disorder/ or /CPAP and panic disorder/ or /OSA treatment and panic disorder/ or /OSA and antidepressants and panic disorder/ or /OSA and benzodiazepines and panic disorder/ or /OSA and antipsychotics and panic disorder/
Filters: clinical trials or reviews, and humans and adults 19 + years, years from January 1990 to December 2022

undifferentiated anxiety (DeZee *et al.* 2005). Lucchini *et al.* (2012) found both panic disorder and OSA in a large sample of patients who responded to the 9/11 World Trade Center disaster.

Studies that have analyzed the prevalence of PD in patients with OSA are summarized in Table 1.

Prevalence of OSA in panic disorder patients

It is also essential to look at the subject from the other side. However, so far, there is no evidence regarding the prevalence of OSA in panic disorder patients.

Mechanisms connected with the comorbidity

Gold *et al.* (2015) support a new theory that combines previous observations regarding chronic stress and sleep-disordered breathing (SDB) as the origin and insomnia and anxiety as consequences. Gold *et al.* (2015) assessed patients for their bodily arousal, the physical symptoms of the sympathetic nervous system component of the stress response, using a validated 17-item questionnaire. Subjects also completed a regular self-assessment of sleepiness and fatigue. Three hundred-two subjects with OSA or UARS (Upper Airway Resistance Syndrome) were extracted for whom baseline evaluation of physical arousal, sleepiness, and fatigue were obtainable for all patients and in 94 patients after CPAP intervention (Gold *et al.* 2014). OSA patients proved comparably increased levels of self-rated bodily arousal (increased stress levels). In both groups, initial physical arousal levels were significantly correlated with sleepiness and fatigue. Bodily arousal was greatly reduced during treatment with CPAP, and sleepiness, fatigue, and a decrease in physical arousal were significantly correlated with a reduction in fatigue. The authors concluded that OSA shares a pathophysiological pathway of lasting stress associated with the nocturnal presence of inspiratory flow limitation (IFL) during sleep, which could be an important reason for their sleepiness and fatigue (Gold *et al.* 2014)

Amdo *et al.* (2016) established the theory that the prevalence of somatic syndromes, anxiety, and insomnia among patients with sleep-disordered breathing (SDB) correlates with bodily arousal and symptoms of increased tone of the sympathetic nervous system. The authors used the Body Sensation Questionnaire (BSQ on 152 patients with UARS and 150 patients with OSA. For the combined number of SDB subjects, the authors modelled the association of BSQ scores with the presence of each factor in each of the three categories adjusted for males and females. The mean BSQ score was substantially higher in women than in men. The BSQ scores significantly positively correlated with prevalence rates of somatic syndromes, anxiety, and insomnia. Women had a higher prevalence of somatic conditions and anxiety than men, while their levels of insomnia were comparable. In subjects with SDB, there was a clear correlation between the intensity of bodily arousal and the incidence of stress-related symptoms such as somatic signs, anxiety, and insomnia (Amdo *et al.* 2016).

Exploring the potential link between behavioural hyperventilation and sleep apnoea (mostly of central aetiology) could be interesting, but systematic studies are missing. Several authors reported a case series of subjects with central sleep apnoea connected with episodes of hyperventilation (Pevernagie *et al.* 2012, Johnston *et al.* 2015). These patients also had daytime hyperventilation and were diagnosed with PD. These findings correspond with the sole meta-analysis, which confirms that subjects with panic disorder have increased minute ventilation and decreased concentration of HCO_3-. This may lead to instability of the

Tab. 1. Summary of original studies about the prevalence of panic disorder in OSA or prevalence of OSA in patients with panic disorder

Name of the study	Sample size	Study design	Methodology	Results
Yue *et al.* 2003	30 OSA patients, 30 matched controls	Case-control study	All patients finished the SCL-90 and the Epworth Sleep Scale (ESS) and were diagnosed via polysomnography	The severity of anxiety in OSA patients negatively correlated to TST and NREM and positively correlated with the percentage of awake time after sleep onset, stage 1 NREM sleep rate, and ESS scores.
Appleton *et al.* 2018	1011 adults	Online survey study	A cross-sectional online survey of OSA patients to assess comorbidities.	Comorbid sleep conditions were common, with 56 % of participants having at least one other sleep disorder. Anxiety was independently associated with diagnosed OSA.
Law *et al.* 2014	101 patients with OSA	Cross-sectional study	Major depressive episodes (MDD), generalized anxiety disorder (GAD), and panic disorder (PD) were evaluated by a diagnostic interview utilizing two questionnaires: HADS and BDI-FS.	PD prevalence was 28.7 %.
DeZee *et al.* 2005	171 patients	Survey	All patients were screened for psychiatric disorders with the Primary Care Evaluation of Mental Disorders before their appointment with the sleep provider.	The most frequent sleep disorder was OSA, with a prevalence of panic disorder at 3 %. A total of 12 % had unspecified anxiety.

Abbreviations: REM, rapid eye movement; OSAS, obstructive sleep apneas; ESS, Epworth Sleepiness Scale, SCL 90, Symptoms Checklist 90; PD, panic disorder, TST, total sleep time

ventilatory centre and an increased risk of central apnoea generation (Grassi *et al.* 2013).

The outcome of CPAP intervention on panic episodes and posttraumatic stress disorder (PTSD) is easily explainable in light of the reduction in BSQ scores detected in patients treated with CPAP (Takaesu *et al.* 2012, Tamanna *et al.* 2013, Gold *et al.* 2015). The model stating that SDB may be a basis of cumulative tension leading to an increase in the prevalence of anxiety consequences explains the main part of the relationship between SDB and anxiety disorders.

Studies that have dealt with the mechanism of comorbidity of panic disorder and OSA are described in Table 2.

Obesity as a link between OSA and panic disorder

Obesity is a risk factor for several conditions, and there is increasing data linking it to mental illnesses (anxiety and depression) (Ahlberg *et al.* 2002). Several mechanisms may explain the associations between psychiatric disorders and obesity, including poor sleep quality, overeating, physical inactivity, and medication usage (primarily antidepressants and antipsychotics). Obesity is associated with a higher risk of OSA, as it increases the probability of airway closure by directly changing the anatomy of the upper airway as fat is placed in adjacent structures and via effects on pulmonary volumes and, therefore, the steadiness of respiratory regulation (Malhotra *et al.* 2002, Patil *et al.* 2004, Faith *et al.* 2011). Obesity can consequently create the basis for a vicious circle, where mental illness increases the risk of OSA and sleep apnea, which worsens mental health (Patil *et al.* 2004).

Influence of the OSA treatment on panic disorder

CPAP treatment of OSA and panic disorder

Regarding panic disorder, CPAP therapy has been reported in a few case studies to attain relief or remission of PD in patients with panic disorder and comorbid OSA (Enns *et al.* 1995, Trajanovic *et al.* 2005). However, systematic evidence of the efficacy of CPAP intervention on panic disorder symptoms was assessed only in an open trial and a randomized cross-sectional study about the efficacy of CPAP intervention in PD in patients with OSA (Edlund *et al.* 1991, Takaesu *et al.* 2012).

Enns *et al.* (1995) and Trajanovic *et al.* (2005) published cases of patients with panic disorder and OSA whose panic attacks diminished after CPAP treatment. Edlund *et al.* (1991) studied the outcomes of CPAP intervention in 16 subjects with PD comorbid with OSA in an open-label study. They stated that CPAP led to the resolution of panic episodes in most of these subjects. These results could lead to the notion that obstructive sleep apnea is a direct reason for panic disorder in some patients. However, Hyun *et al.* (2019)

found an increased rate of non-adherence to the CPAP among patients with OSA and comorbid panic disorder, and the low adherence resulted in non-improvement of the anxiety symptoms.

Takaesu *et al.* (2012) investigated the efficacy of CPAP in subjects with panic disorder comorbid with OSA in a randomized cross-sectional study utilizing sham CPAP as a control condition. Subjects with panic disorder (n = 12) with AHI (Apnoe/Hypopnoea Index) higher than 20/h completed the study. Patients were requested to keep their seizure frequency histories and Panic Disorder Severity Scale (PDSS) scores. Then subjects participated in a randomized crossover experimental interval measuring normal CPAP and sham CPAP throughout night sleep for four weeks. There were significant reductions in panic attack frequency, PDSS total score, and incidence of alprazolam usage for symptom relief compared to baseline conditions or sham CPAP. These results suggest that OSA contributes to the symptomatology of panic disorder. A combination of pharmacological and OSA-specific interventions, such as CPAP, might be suggested for patients with panic disorder comorbid with OSA (Takaesu *et al.* 2012). Since all subjects in this paper reported that the onset of their OSA symptoms preceded the beginning of panic disorder, the possibility that OSA contributes to the development of panic disorder should be considered. However, the complete remission of seizures was not observed (Takaesu *et al.* 2012).

Studies that have dealt with CPAP treatment in subjects with OSA and PD are shown in Table 3.

Fear of CPAP mask and panic disorder in OSA treatment

Despite the well-known positive outcomes of CPAP on many symptoms and comorbidities, some patients cannot use the treatment for various reasons. Adherence to CPAP treatment is generally characterized as using it for more than 4 hours per night on seventy per cent of nights. Non-adherence is very common (17-28% of patients) for various reasons; the treatment bothers the patient (for example, the mask leaks) (Sawyer *et al.* 2011). The distress of choking can be more widespread in severe OSA (Rezaeitalab *et al.* 2014). Claustrophobia is one of the underdiagnosed treatment-specific barriers frequently met in the clinical setting and debated in the literature. Claustrophobia includes fear of restriction and suffocation and can be provoked by applying a CPAP mask on the face (Rachman & Taylor 1993). Claustrophobic tendencies in CPAP treatment are more often in women and patients with higher BMI (Edmonds *et al.* 2015). It is necessary to talk to the patient and recognize the symptoms of anxiety and panic during treatment, which is crucial in the first days and months of treatment. In such a case, it is possible to manage the initiation of therapy and thus achieve all the mentioned positive effects of this treatment. Several approaches can be used, including cognitive behavioural therapy and a nasal instead of an oronasal mask (Edmonds *et al.* 2015).

Influence of the panic disorder treatment on obstructive sleep apnoea

Several commonly used antidepressants and anxiolytics can significantly disrupt sleep architecture, and the hypnotic effect of several of them can negatively affect sleep breathing disorders.

Antidepressants

Antidepressants (ADs) are commonly used in the therapy of panic disorder. Many OSA patients also take antidepressants, as reflected in several studies. The use of antidepressant medication is related to a higher

Tab. 2. Summary of original studies about mechanisms connected with the comorbidity of OSA and panic disorder

Name of the study	Sample size	Study design	Methodology	Results
Gold *et al.* 2015	152 UARS and 150 OSA patients	Retrospective study	Measuring the BSQ scores and comparing them with FSS and ESS In patients treated with nasal CPAP, change in FSS and ESS scores with differences in BSQ scores were correlated.	FSS and ESS scores are positively associated with the BSQ score. CPAP treatment reduced all three patient questionnaire scores, and differences in FSS were significantly associated with differences in BSQ.
Amdo *et al.* 2016	152 UARS and 150 OSA patients	Comparative study	BSQ was used in 152 UARS subjects and 150 OSA subjects. Patients, according to symptoms, were divided into three categories: somatic syndromes, anxiety, and insomnia.	BSQ scores in women were substantially higher than in men (32.5 ± 11.1 vs 26.9 ± 8.2; mean ± SD). Rising BSQ scores are connected significantly with rising prevalence levels of somatic signs ($p < 0.0001$), anxiety ($p < 0.0001$), and insomnia ($p \leq 0.0001$). Women had greater prevalence levels of somatic syndromes and symptoms of anxiety than men at any BSQ count, while levels of insomnia were comparable.

Abbreviations: UARS, upper airway resistance syndrome; OSA, obstructive sleep apnea; BSQ, body sensation questionnaire; FSS, the fatigue severity scale; ESS, Epworth sleepiness scale; CPAP, continuous positive airway pressure

Tab. 3. Summary of original studies about CPAP treatments of OSA and panic disorder

Name of the study	Sample size	Study design	Methodology	Results
Enns *et al.* 1995	1	Case report	–	Remission of PD after CPAP treatment, effect present in 6 months follow-up.
Trajanovic *et al.* 2005	1	Case report	–	Remission of nocturnal panic attacks after CPAP treatment, effect present in a 9-month follow-up.
Edlund *et al.* 1991	16 patients with panic attacks in a larger sample (n=301)	Survey	A structured interview with patients who had panic attacks and OSA.	Panic attacks remission in all subjects with CPAP intervention.
Takaesu *et al.* 2016	12 PD patients with OSA	Prospective study	The incidence of episodes and count on the panic disorder severity scale (PDSS) were assessed, randomized crossover trial period with CPAP and a sham group for four weeks was conducted.	The incidence of panic episodes, total PDSS score, and the incidence of alprazolam usage for relieving the symptoms significantly reduced throughout the CPAP treatment.

Abbreviations: PD, panic disorder; CPAP – continuous positive airway pressure; OSA, obstructive sleep apnea; PDSS, the panic disorder severity scale

probability of comorbid OSA, especially in patients who also take antihypertensive medication and suffer from depressive symptoms or excessive sleepiness (Farney *et al.* 2004). In addition to treating anxiety and depressive symptoms, antidepressants are given to OSA patients to treat sleep disorders. Guilleminault et al. (2006) found in their patients that ADs are administered as often for insomnia as for depressive symptoms. In the trial treatment of OSA with antidepressants, an improvement in scores in the ESS (Epworth Sleepiness Scale) and BDI (Beck's Depression Inventory) questionnaires were noted, although smaller than in the CPAP treatment (Taskin *et al.* 2010).

Several studies have dealt with treating antidepressants in patients with panic disorder and OSA (Table 4).

Tricyclic antidepressants

TCA use has been described to result in nearly a 10% reduction in REM sleep (Smith *et al.* 2006). Because apneas occur more often in REM sleep, reducing this phase could provide a protective instrument against respiration-induced arousal (Smith *et al.* 2006, DeMartinis & Winokur 2007). However, the clinical significance of REM suppression can be changed in the intensity and frequency of dreaming and a probable negative effect on memory and learning (DeMartinis & Winokur 2007). Therefore, TCAs are not the first choice for patients with OSA.

SSRI

Serotonin levels have been reduced in depressed patients and certain sleep states that may increase OSA symptoms (Smith *et al.* 2006). In the therapy of OSA, SSRIs have been promoted to reduce REM sleep and improve upper airway dilator tension by increasing serotonin levels (Kraiczi *et al.* 1999, Smith *et al.* 2006).

Fluoxetine

Fluoxetine considerably reduced REM sleep and decreased AHI scores throughout non-REM sleep (Hanzel *et al.* 1991, Prasad *et al.* 2010). Nonetheless, there was no decrease in AHI during REM sleep nor a reduction in oxygen desaturation and arousal. Prasad *et al.* examined whether using fluoxetine in a mixture with a drug that inhibits 5-HT3 receptors (ondansetron) could be beneficial. However, no significant development in OSA-related symptoms was reported in patients treated with this combination compared to placebo (Prasad *et al.* 2010).

Paroxetine

In a placebo crossover study of 20 patients, paroxetine 20 mg decreased AHI during non-REM sleep but demonstrated no significant impacts on psychopathological or OSA-related daytime signs (Hanzel *et al.* 1991).

Sertraline

Remarkably, in another study on subjects with coronary heart disease, the therapy with sertraline in treating depression in OSA subjects was ineffective (Roest *et al.* 2011). However, the effects of sertraline on OSA were not evaluated in this work.

These studies show that endogenous brainstem serotonin stimulates upper airway enlargement throughout wakefulness, whereas peripheral serotonin release promotes REM-related apnea.

Tab. 4. Summary of original studies about the influence of antidepressants in panic disorder treatment on obstructive sleep apnoea

Name of the study	Drug	Sample size	Study design	Methodology	Results
Kraiczi *et al.* 1999	Paroxetine (SSRI)	20 male OSA patients	A double-blind, randomized, placebo-controlled crossover study	Assessment of the impact of paroxetine (20 mg od) on polysomnographic and psychopathologic consequences in OSA subjects.	Paroxetine decreased the apnea index throughout NREM sleep but not during REM sleep, and no effect on hypopnea was observed. Correspondingly, the impact of paroxetine on apnea was not connected with the substantial overall improvement in psychopathologic scales.
Hanzel *et al.* 1991	Fluoxetine (SSRI) compared to protriptyline (TCA)	12 patients with OSA	A clinical trial, Prospective crossover unblinded trial	Comparing TCA protriptyline to SSRI fluoxetine in the therapy of OSA.	Fluoxetine significantly reduced REM sleep time and the number of apneas or hypopneas in NREM sleep. No significant decrease in the number of arterial oxygen desaturation events was observed.
Prasad *et al.* 2010	Fluoxetine (SSRI) (and ondansetron)	35 adults with (AHI) > 10; range 10-98	Prospective single-centre trial in subjects with OSA	Subjects were randomized to placebo and fluoxetine, and ondansetron groups.	OND+FL caused a nearly 40% decrease in baseline AHI-improved oximetry readings. This treatment-associated relative decrease in AHI was also observed in REM sleep.
Roest *et al.* 2012	Sertraline (SSRI)	105 with coronary heart disease and current major depressive disorder	Secondary analysis of data from a randomized, double-blind, placebo-controlled clinical trial	One hundred five patients with coronary heart disease and major depressive disorder were randomized to receive sertraline plus either omega-3 or placebo for ten weeks.	Thirty of the 105 subjects (29 %) were categorised as having moderate to severe OSA based on nighttime heart-rate patterns. Patients with OSAHS reported greater item scores at follow-up on all depressive symptoms measured with the BDI-II compared to those without OSA.
Carley *et al.* 2007	Mirtazapine	7 men and 5 women with newly diagnosed (treatment-naive) and uncomplicated OSA	Randomized, double-blind, placebo-controlled, 3-way crossover study	Each subject took medication before bedtime each night for three consecutive 7-day treatment periods. These treatments comprised (1) placebo, (2) 4.5 mg per day of mirtazapine, and (3) 15 mg per day of mirtazapine. Subjects underwent polysomnography after 7 days of taking medication.	Concerning placebo therapy, 4.5 mg of mirtazapine substantially lowered the AHI in all sleep phases to 52%, and 15 mg of mirtazapine lowered the AHI to 46%. Sleep fragmentation was relieved only by the higher dose of mirtazapine. Significant differences in the macro-architecture of sleep were not found in any group.
Marshall *et al.* 2008	Mirtazapine	20 and 65 patients with OSA	Two randomized, double-blind, placebo-controlled trials of mirtazapine for OSA	a dose-finding study assessing the self-administration of mirtazapine (7.5, 15, 30, and 45 mg) or placebo 30 minutes before bedtime for two weeks at each dose.	No quality of sleep apnea improved due to mirtazapine in the study. Weight gain was considerably more significant on mirtazapine than on placebo.
Waterman *et al.* 2016	Venlafaxine	468 adults ≥60 years old with the major depressive disorder; 80 of them had OSA as well	Comparative clinical trial	Adults with major depressive disorder. Participants were questioned if they had been diagnosed with OSA using PSG to assess the presence of OSA.	Eighty participants (17.1 %) reported a diagnosis of OSA. Subjects with OSA were more likely to be men, report more significant health damage, have a longer episode duration, and receive a fair antidepressant trial before entering the study. 40.8 % responded to venlafaxine therapy of the non-OSA group and 27.5 % of the OSA group. Participants without OSA were 1.79 times more likely to respond to therapy than those with OSA.

Abbreviations: AHI – apnoea/hypopnoea index, SSRI – selective serotonin reuptake inhibitors, OSA- obstructive sleep apnea, OND-ondansetron, FL – Fluoxetine, TCA – tricyclic antidepressants, SSRI- selective serotonin reuptake inhibitors, PSG, polysomnography

Other types of antidepressants

Venlafaxine

Venlafaxine is an antidepressant of the SNRI group, which is also used to treat panic disorder. Waterman *et al.* investigated the effect of venlafaxine in older patients with depression and noted that comorbidity with OSA predicted less efficacy of the antidepressant medication. However, they do not have data on the anxiety issue (Waterman *et al.* 2016).

Mirtazapine

Carley *et al.* examined whether mirtazapine would be beneficial in patients with OSA. After one week of therapy, the mean AHI decreased from 22.3 to 13.5 and 11.4 per hour on the 4.5 and 15 mg doses, respectively. Sleep efficacy and percentage of REM sleep were substantially increased by the 15 mg/day dose (Carley *et al.* 2007). Marshall *et al.* further investigated the usage of mirtazapine in OSA in two separate randomized, double-blind, placebo-controlled trials. Both studies did not change the amount of time spent sleeping or the AHI. In addition, both studies showed a considerable rise in weight in subjects receiving mirtazapine in all groups, which could further exacerbate OSA (Marshall *et al.* 2008).

AbdelFattah *et al.* (2020) summarized the consequences of antidepressants on ventilatory parameters in OSA. All antidepressants (TCAs, tetracyclic, SSRIs, and serotonin receptor modulators) showed positive effects on the respiratory parameter AHI. On the other hand, no effect was noted on OSA scales, such as sleep quality and daytime sleepiness (AbdelFattah *et al.* 2020).

Anxiolytics

Some benzodiazepine receptor agonists used to treat panic attacks could worsen OSA by curbing the respiratory muscle tone of the upper airways (Hanly & Powles 1993).

Benzodiazepines

The usage of benzodiazepines in OSA subjects should be restricted due to their recognized danger of causing decreased upper airway muscle tone and reduced ventilatory answer to hypoxia, hypothetically increasing AHI and lengthening apnea (Nakayama *et al.* 2013, Oğuztürk *et al.* 2013, Sharafkhaneh & Hirshkowitz 2012, Medina 2018). If airway obstruction happens, ventilation is restored in reply to CNS excitation, which permits the patient to wake up to expand the airway freely. The more sedated the subject is, the more complicated it is to wake them up and the lengthier it is to reopen the airway. A study by Wang *et al.* (2019) discovered an increased risk of respiratory failure in patients with OSA who were also taking BZDs. Interestingly, *both short-term and long-term use of BZD represented a higher risk* (Wang *et al.* 2019). Gonçalves *et al.* also confirmed the association of BZDs with deeper hypo-saturation in patients with OSA, but only in mild and moderate disorder severity (Goncalves *et al.* 2013).

Despite this, using BZDs in OSA patients could be more exceptional. For example, in one research, 19 % of subjects with suspect OSA (a total sample = 58) used BZDs (Martinez *et al.* 2017). Gonçalves *et al.* (2013) found 26.6% of BZD users in their sample of OSA patients. Another study on already diagnosed OSA patients in Sweden reported a prevalence of BZD use (confirmed by positive urinary BZDs) in 3.2% of their sample. These findings were not different from the usage of BZD in the general population (Nerfeldt *et al.* 2004).

Hypnotics

Non-benzodiazepine medications such as zopiclone, zolpidem, and eszopiclone have hypnotic and sedative outcomes comparable to benzodiazepines. However, several have lesser relaxing outcomes; therefore, they could be more suitable for the short-term management of insomnia in OSA. Literature documents using zolpidem up to 10 mg did not obstruct using CPAP in subjects with severe OSA. As a benefit, there was a decrease in sleep onset latency and mean arousal index (Krakow *et al.* 2004). Another study with zolpidem confirmed that despite a slight shortening of REM sleep, phase 2 was almost unchanged and phases 3-4 were prolonged. There were no feelings of sleepiness during the day (Cirignotta *et al.* 1988).

As the overall quality of sleep depends mainly on the number of awakenings, the short usage of non-benzodiazepines is considered a safe and effective approach for enhancing adherence to CPAP in subjects with comorbid psychiatric disorders (Declerck *et al.* 1993, Takesu *et al.* 2012, Lettieri *et al.* 2009). Zhang *et al.* (2014) analyzed clinical studies that assessed objective sleep quality and parameters of OSA severity (AHI, saturation). A total sample of 488 patients had a substantial improvement in sleep in patients with a non-benzodiazepine hypnotic compared to placebo, without worsening OSA parameters. (Zhang *et al.* 2014).

Antipsychotics

The usage of antipsychotics is related to a nearly doubled risk of severe OSA, probably due to irregular upper airway tone or change in respiratory control (Lin & Winkelman 2012). As obesity is one of the main causing factors of OSA, drug-induced weight gain, a recognized side effect of many antipsychotics, may lead to developing or aggravating OSA symptoms (Lin & Winkelman 2012, Khazaie *et al.* 2018). Avinash and Rothali (2020) found an association between a potential OSA development and a higher risk of metabolic syndrome in patients who used atypical antipsychotics for three months or more.

On the other side, Khazaie *et al.* (2018) further examined the effect of individual antipsychotics (olanzapine,

risperidone, and quetiapine) on respiratory parameters in subjects with paradoxical insomnia. While the apnea index did not change much (except for patients treated with quetiapine), a significant change was noted in the hypopnea index and AHI. Remarkably, Shirani *et al.* (2011) found that antipsychotics in patients with depression, but not those with other psychiatric disorders, seemed to raise the OSA risk after adjusting for identified predisposing factors.

CONCLUSION

Both panic disorder and obstructive sleep apnea are frequent in the general population, and the relationship between the two conditions seems bidirectional. Although both disorders are often comorbid in clinical settings, there is scarce evidence in contemporary literature shedding light on the connection. It is necessary to assess OSA patients for comorbid panic disorder and vice versa. Both conditions can worsen the other and must be treated with a complex approach to ensure improvement in the patient's physical and psychological health.

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