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REVIEW

Obstructive sleep apnea: management considerations in psychiatric patients

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Taryn Heck[1]
Monica Zolezzi[2]

[1]Pharmacy Department, University of Alberta Hospital, Alberta Health Services, Edmonton, AB, Canada; [2]Clinical Pharmacy and Practice, College of Pharmacy, Qatar University, Doha, Qatar

Abstract: Psychiatric disorders and obstructive sleep apnea (OSA) are often comorbid. However, there is limited information on the impact of psychotropic medications on OSA symptoms, on how to manage psychiatric pharmacotherapy in patients presenting with OSA, or on the effectiveness and challenges of OSA treatments in patients with comorbid mental illness. As such, the objective of this article is to provide an overview of some epidemiological aspects of OSA and treatment considerations in the management of OSA in individuals with comorbid psychiatric disorders. Predefined keywords were used to search for relevant literature in electronic databases. Data show that OSA is particularly prevalent in patients with psychiatric disorders. The medical care that patients with these comorbidities require can be challenging, as some of the psychiatric medications used by these patients may exacerbate OSA symptoms. As such, continuous positive airway pressure continues to be the first-line treatment, even in patients with psychiatric comorbidity. However, more controlled studies are required, particularly to determine continuous positive airway pressure compliance in patients with mental illness, the impact of treating OSA on psychiatric symptoms, and the impact of the use of psychotropic medications on OSA symptoms.

Keywords: obstructive sleep apnea, psychiatric disorders, comorbidity, psychotropic medications

Background

Obstructive sleep apnea (OSA) is a clinical syndrome in which a person recurrently stops breathing throughout his or her sleep.[1] These interruptions in breathing are caused by an upper airway obstruction as a consequence of inadequate motor tone of the tongue and/or airway dilator muscles. Patients may experience partial (hypopnea) or complete (apnea) occlusion of airflow. With each period of apnea that the patient experiences, a reduction in blood oxygen levels (hypoxia) occur, causing arousals and fragmented sleep. Common symptoms include daytime sleepiness, fatigue, irritability and impaired cognitive function which have been linked to an increased risk of motor vehicle collisions and work-related injuries.[2,3] Furthermore, sleep apnea is associated with serious health conditions including obesity, cardiovascular disorders such as hypertension, ischemic heart disease, arrhythmia, and heart failure; cerebrovascular disease; and endocrine disorders including the metabolic syndrome.[4–7]

In addition to the serious health conditions previously described, psychiatric disorders and OSA are also frequently comorbid, especially with depression.[8] It has been suggested that the mood disturbance may represent a consequence of sleep apnea; but it is also argued that psychiatric disorders and their pharmacological treatment may contribute to and promote the development of sleep apneas.[9] Medications with inhibitory effects on the central nervous system (CNS) such as benzodiazepine receptor agonists, barbiturates, antiepileptic drugs, sedating antidepressants, antihistamines,

Correspondence: Monica Zolezzi
College of Pharmacy, Qatar University,
PO Box 2713, Doha, Qatar
Tel +974 44 035 623
Fax +974 44 035 551
Email mzolezzi@qu.edu.qa

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and opiates, all of which are commonly used in patients with psychiatric disorders, may also have an impact on sleep quality and architecture, and thus can worsen or further exacerbate the symptoms of OSA.[10,11]

However, there is currently a paucity of data evaluating the impact of psychotropic medications on OSA symptoms, on how to manage psychiatric pharmacotherapy in patients presenting with OSA, or on the effectiveness and challenges of OSA treatments in patients with comorbid mental illness. As such, the objective of this article is to provide an overview of some epidemiological aspects of OSA and treatment considerations in the management of OSA in individuals with comorbid psychiatric disorders.

Methods

A literature search on PubMed, Medline, Embase, Cochrane Database, and International Pharmaceutical Abstracts was conducted for relevant English-language articles from 1980 to June 2015. The main search keywords included the following: ["therapy" OR "treatment" OR "therapeutics"] AND ["sleep apnea" OR "obstructive sleep apnea"] AND ["psychiatry" OR "psychiatric patients" OR "psychiatric disorders"], and ["mental health" OR "mental health patients" OR "mental health disorders"]. The search was restricted to review publications in the adult patient population. Additional articles in relation to the treatment of OSA in the psychiatric population were obtained by manually searching the guidelines, the bibliography of retrieved review articles, and the position papers of relevant national or international association Web sites. A total of 80 articles were selected for this review.

Risk factors, screening, and diagnosis of OSA

The prevalence of OSA is higher in patients who have a combination of the following risk factors: obesity, neck larger than 17 inches for men or 16 inches for women, male sex, age ≥40 years, large tonsils, or recessed chin.[12] Differences in the structure and physiological behavior of the upper airway, in craniofacial morphology, and in the pattern of fat deposition between the sexes have been proposed to account for a higher male risk of OSA.[13–15] It is imperative that at-risk patients be screened and appropriately treated to prevent complications, as untreated OSA is currently recognized as an independent risk factor for mortality.[1]

Patients who present with or describe signs and symptoms of choking or gasping during sleep, repeated awakenings from sleep, unrefreshing sleep, daytime fatigue, and impaired concentration should be suspected of having OSA. While men often report symptoms such as snoring, waking up gasping for air or snorting, many women report symptoms like fatigue, anxiety, and depression.[15]

Because the clinical features are nonspecific and the diagnostic accuracy of clinical impression alone is poor, a variety of clinical questionnaires and scores have been developed to assess patients with common signs and symptoms of OSA. The Epworth Sleepiness Scale (ESS), which is used to subjectively assess pretreatment sleepiness, is a self-administered questionnaire that consists of eight scenarios, wherein patients rate whether there is a high chance of their dozing or falling asleep in that particular situation.[16] Another validated tool to screen patients for OSA is the STOP and the STOP-BANG questionnaires (the latter having a higher sensitivity).[17] STOP-Bang involves questions pertaining to Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, and Sex.

Depending on level of urgency, which is ranked by suspicion of OSA, the screening score, the individual's occupation, and the presence of comorbidities, most recent guidelines recommend polysomnography (PSG) for diagnostic testing.[14,18,19] The diagnosis of OSA is based on the presence or absence of related symptoms, as well as the frequency of respiratory events during sleep (ie, apneas, hypopneas, and respiratory-effort-related arousals) as measured by a standardized facility-based PSG. The primary outcome measure of PSG is the apnea–hypopnea index (AHI), which is the average number of disordered breathing events per hour. Typically, OSA is defined as an AHI of 5 or greater with associated symptoms (eg, excessive daytime sleepiness, fatigue, or impaired cognition) or an AHI of 15 or greater, with or without associated symptoms.[1,14,20]

Management of OSA

Guidelines for the management of OSA recommend continuous positive airway pressure (CPAP) as the first treatment of choice.[20–22] A CPAP machine provides a constant flow of air at a pressure that maintains an open upper airway via a mask on either the mouth and/or nose.[1,14] When compared with controls, CPAP use in patients with moderate and severe OSA has shown significant improvements in sleepiness, quality of life, cognitive function, and 24-hour blood pressures.[23] Despite its well-recognized benefits, CPAP acceptance and adherence remain problematic.[1,14,24] Education and support for patients who are experiencing difficulties have been reported to respond favorably and improve adherence.[1,14,24]

Other alternative nonpharmacological treatments are oral appliances, weight loss, and surgery.[25,26] Oral appliances are

an alternative for patients with mild-to-moderate OSA who are unable to tolerate CPAP therapy.[1,14] Appliances exhibit their effect by causing displacement of the mandible, which expands the diameter of the upper airways.[23] Common to all guidelines is the recommendation that weight loss should be encouraged in all obese patients diagnosed with OSA.[21,22,26] It is important, however, that attempts to lose weight should not delay the initiation of CPAP when indicated.[21] Surgery may also be an option for some OSA patients. The type of surgery required varies depending on which particular part of the patient's airway is blocked.[25]

A number of pharmacological agents have been investigated for the treatment of OSA.[27] However, most guidelines do not recommend pharmacological agents as first-line therapies for OSA.[21,22] Nonetheless, the guidelines and a few reports also highlight that relief of nasal obstruction and agents that promote wakefulness may be useful adjuncts in the treatment of patients with OSA to either facilitate treatment with CPAP or help decrease daytime sleepiness despite other therapies.[14,21,22,28]

Comorbidity of OSA in patients with mental illness

Overall, the evidence is stronger and is rapidly building for an association of OSA with depression and anxiety. In a large cohort study of patients with sleep apnea, psychiatric comorbidity included depression (21.8%), anxiety (16.7%), posttraumatic stress disorder (PTSD) (11.9%), psychosis (5.1%), and bipolar disorders (3.3%).[9] A recently published systematic review indicated that there may be an increased prevalence of OSA in individuals with major depressive disorder and with PTSD.[29] Another recent retrospective study found that there is a significant increased likelihood of being diagnosed with OSA and a mood disorder (odds ratio [OR] =1.85; 95% confidence interval [CI] =1.71–1.72) or an anxiety disorder (OR =1.82; 95% CI =1.77–1.84).[8] Notably, this positive relation remained after accounting for severity of body mass index. Other authors have also reported positive correlations between anxiety and depression in patients with OSA.[30–34]

In a systematic review of the literature, Youssef et al indicated that the prevalence of OSA in patients with attention deficit hyperactivity disorder (ADHD) is higher than in the general population, approximately 25%–30% versus 3%, respectively.[35] In another more recent study, although ADHD was not a frequent illness in adult patients with OSA, those with OSA and ADHD showed higher levels of anxiety and daytime sleepiness and poorer quality of life than in those without ADHD.[36] Although OSA and insomnia appear to be opposing conditions based on the indicators of alertness and sleepiness, as pointed out by Luyster et al,[37] numerous studies have found that these two conditions frequently coexist, with 39%–54.9% of patients with OSA either meeting criteria for insomnia or displaying insomnia symptoms as defined by the individual studies.[37]

There seems to be insufficient evidence to support increased OSA in schizophrenia or in bipolar disorder;[29] however, individuals with these conditions are known to be at an increased risk for metabolic syndrome and obesity, which are also important risk factors for OSA.[38–40] Although a causal relationship between OSA and Alzheimer's disease (AD) has not been established, in a recent review of the literature, authors indicated that the sleep fragmentation and intermittent hypoxia that occurs in OSA could promote cognitive dysfunction, overlapping with that in AD and other neurodegenerative diseases.[41]

Psychotropic medications and the management of OSA

Antipsychotics

OSA is often overlooked in the context of schizophrenia, because its hallmark symptom, daytime sleepiness, is so easily attributable to antipsychotic medications.[38] The use of atypical antipsychotics is associated with a near doubling of the risk of severe OSA, possibly due to an induction of abnormal upper airway tone or alteration in respiratory control secondary to dopamine receptor antagonism.[42] As obesity is one of the main precipitating factors of OSA, medication-induced weight gain, a well-known side effect from atypical antipsychotics, can lead to worsening or exacerbating OSA symptoms.[38] Interestingly, Shirani et al found that the use of atypical antipsychotics in subjects with depression, but not in those with other psychiatric diagnoses, appeared to increase the risk of OSA after controlling for known predisposing factors.[43]

Antidepressants

Various types of antidepressants have been investigated for the treatment of OSA, and, as depression has been linked with OSA, treatment with a tricyclic antidepressant (TCA), selective serotonin receptor inhibitor (SSRI), or another form of serotonergic agent may provide benefits for both of these diseases. The use of TCAs has been reported to result in an approximately 10% decrease in rapid eye movement (REM) sleep.[10] As apneas tend to more frequently occur in REM sleep, a decrease in this stage provides a protective mechanism against respiratory-related arousals.[10,44] However, clinical consequences of REM suppression can be a change in frequency and intensity of dreaming, as well as a possible

negative effect on memory and learning.[44] Protriptyline has been the most studied TCA in OSA patients. Three crossover studies published in the 1980s comparing protriptyline to placebo demonstrated a nonsignificant improvement in objective apnea parameters or symptoms.[45–47]

It has been reported that the levels of serotonin are reduced in patients with depression and in certain sleep states that can cause augmentation of OSA symptoms.[10] In the management of OSA, SSRIs have been advocated to produce a reduction in REM sleep as well as improving upper airway dilator tone through an increase in serotonin levels.[10,48] When compared with protriptyline, fluoxetine significantly reduced REM sleep and significantly improved the AHI score during non-REM sleep.[48] However, there were no significant improvements in AHI during REM sleep, or in oxygen desaturations and arousals. In another placebo crossover trial involving 20 patients, paroxetine 20 mg taken orally once daily for 6 weeks reduced AHI during non-REM sleep (−35%, P=0.003) but showed no significant effects on psychopathologic- or OSA-related daytime symptoms.[49] Interestingly, in another study in patients with coronary artery disease, the use of sertraline was ineffective in managing depression in patients with OSA.[50] However, the effects of sertraline on the symptoms of OSA were not assessed in this study.

On the basis of these findings that endogenous serotonin release in the brainstem promotes upper airway dilation during the awake state while peripheral serotonin release at 5-HT_3 receptors promotes REM-related apnea, Prasad et al tested if using an SSRI (fluoxetine) in combination with a medication that inhibits 5-HT_3 receptors (ondansetron) would be advantageous.[51] However, patients treated with the combination did not report significant improvement in OSA-related symptoms versus those on placebo. In another study, Carley et al investigated whether mirtazapine, a mixed $5HT_2$ and $5HT_3$ antagonist, would have beneficial effects for OSA patients.[52] After 1 week of treatment, the mean AHI decreased from 22.3 for placebo treatment to 13.5 and 11.4 per hour for 4.5 and 15 mg doses, respectively (P<0.004). In addition, sleep efficiency and REM sleep percentage were significantly increased by the 15 mg per day dose (P=0.04). Marshall et al further researched the use of mirtazapine in OSA by reporting on two separate randomized, double-blind, placebo-controlled trials.[53] Across both studies, there was no significant difference in the amount of time spent asleep or in AHI. Additionally, there was a significant increase in weight in patients taking mirtazapine across all treatment groups in both studies, which may worsen OSA.

Sedative/hypnotics

Benzodiazepines and other sedatives or hypnotics may be used for insomnia or anxiety in patients with diverse psychiatric conditions. The use of benzodiazepines in patients with OSA has been limited because of their known risk of causing reduced upper airway muscle tone and decreased ventilatory response to hypoxia, thus potentially increasing the AHI and prolonging apnea events.[36,54] If an airway obstruction occurs, ventilation is resumed in response to CNS arousal that allows the patient to awaken to voluntarily dilate the airway. The more sedated the patient is, the more difficult it is to rouse and consequently the longer it takes to reopen the airway.

Nonbenzodiazepine agents, such as zopiclone, zolpidem, and eszopiclone, have hypnotic and sedative effects similar to those of benzodiazepines, but some have fewer muscle-relaxant effects; thus, they may be preferable to use in the short-term management of insomnia in OSA.[11,36] Studies have documented that the use of zolpidem in doses up to 10 mg did not impede the use of CPAP in patients with severe OSA; however, there was a reduction in sleep latency and mean arousal index.[55] For this, benzodiazepines and any medication that may cause sedation, including opioids or sleeping aids, should be used with caution in patients with OSA and should be closely monitored, particularly when titrating doses.[11] The short-term use of nonbenzodiazepine agents has been advocated through various studies as a safe and effective strategy for improving compliance with CPAP in patients with comorbid psychiatric disorders.[55–57]

Stimulants

Psychostimulant medications are associated not only with disrupted or disturbed sleep, but also, paradoxically, calm some patients with ADHD to sleep by alleviating their symptoms.[58]

Studies using modafinil, a nonamphetamine stimulant medication used in the treatment of ADHD, have shown significant reduction of excessive daytime sleepiness associated with OSA in both objective and subjective measures with this medication.[59,60] In most guidelines, modafinil is recommended for use in patients who have residual daytime sleepiness despite optimal use of CPAP.[20–22,26,28,61]

Despite the aforementioned benefits of modafinil as adjunct therapy, its use is associated with some risks, including cardiovascular complications, dependency, and abuse potential. Heitmann et al studied blood pressure effects of modafinil in patients with OSA.[62] The effect on blood pressure was not significant between modafinil and placebo, but

as this study occurred over a very short period of time, the long-term cardiovascular implications require further investigation. Because of the greater risk of dependency and abuse with stimulant medications, they are not recommended for the treatment of OSA at this time.[20–22]

Miscellaneous

As rates of smoking are at least two times higher among patients with psychiatric disorders,[63] the value of nicotine replacement products for patients with both psychiatric disorders and OSA was also researched. Nicotine may improve OSA by stimulating respiration and oropharyngeal muscles.[64] A small study of eight patients by Gothe et al found that the use of 2 and 4 mg nicotine gum significantly reduced the number of apneas, during both the first and second hour of sleep.[65] However, studies looking at other forms of nicotine administration, such as transdermal patch, did not show any effect on AHI.[66] As nicotine acts as a stimulant, it has been reported that sleep efficiency and sleep architecture are negatively affected in these studies.[63,67] Therefore, although smoking cessation should be promoted and encouraged among patients with mental illness, the use of nicotine strictly for the treatment of OSA has not been reported to offer clear benefits.

Of particular importance is the avoidance, or reduction, of alcohol intake. Ingestion of alcohol before sleep has been shown to increase upper airway collapsibility, therefore, precipitating obstructive apneas and hypopneas during sleep.[67] The severity of the effects of alcohol on OSA is controversial, likely due to the variation in amounts that patients may consume prior to sleep. Peppard et al found that relative to men who drank less alcohol, for each increment of one drink per day, there was a 25% greater odds of worsened episodes of sleep apnea (P=0.006).[68] For this reason, avoidance (or moderation if avoidance is not possible) of alcohol should be encouraged for patients diagnosed with OSA.

CPAP for the management of OSA in patients with mental illness

No controlled studies have exclusively focused on the use of CPAP in patients with severe mental illness; however, there are case reports describing improvement in both OSA and psychiatric symptoms with the use of CPAP in patients with schizophrenia.[69–71]

Unlike in schizophrenia and bipolar disorder, the use of CPAP in patients with comorbid depression and/or anxiety disorders has been extensively studied. El-Sherbini et al found a significant reduction in depressive symptoms as determined by the Hamilton Depression Rating Scale and improvement in ESS scores (11.6±8.6 to 5.1±3.1) after CPAP treatment for 2 months.[72] In a recent systematic review of the literature and meta-analysis, Povitz et al reported that CPAP improved depressive symptoms compared to the control intervention (usually sham CPAP) but revealed considerable variability between trials.[73] Notably, CPAP treatment resulted in a greater improvement in depressive symptoms in trials in which there was a high prevalence of depression at baseline than in trials in which there was a low prevalence of depression at baseline. CPAP has also been reported to be effective in OSA patients with comorbid PTSD, showing reduction in PTSD-associated nightmares and improving the overall PTSD symptoms.[74] Similarly, when it was used in patients with panic disorder, CPAP showed positive outcomes in the severity and the frequency of panic attacks.[56] Likewise, in patients with ADHD, Youssef et al investigated the effects of CPAP treatment on ADHD and established that in six interventional studies, either improvement or resolution of ADHD occurred after treatment with CPAP or surgery.[34]

Krakow et al examined the effect of CPAP, oral appliances, or surgery on sleep measures in patients with chronic insomnia and episodes of sleep apnea who completed a cognitive behavior therapy program.[55] Both treatment phases (cognitive behavior therapy alone or in combination with OSA treatment of CPAP, oral appliance, or surgery) resulted in improvements in insomnia severity and sleep-related daytime impairments; however, cognitive behavior therapy alone had a small effect on daytime impairments.

The current literature review also revealed only a few case reports of CPAP-induced psychiatric relapse, one in a previously stable chronic schizophrenic as well as emergent manic episodes in patients with bipolar disorder.[75,76] As previously discussed, compliance with CPAP is challenging; however, this has not been extensively evaluated in patients with psychiatric disorders.[29] Some studies have demonstrated adequate CPAP compliance in patients with PTSD and AD.[77,78] Some studies have also reported on the negative influence of the presence of depression during the CPAP titration trial and on the presence of untreated insomnia symptoms on CPAP compliance.[79,80] However, further studies are needed to clarify whether the treatment of depression and insomnia symptoms leads to a benefit in CPAP compliance.

Conclusion

OSA is particularly prevalent in patients with psychiatric disorders. The medical care that patients with these comorbidities require can be challenging as some of the psychiatric medications used by these patients may worsen

or exacerbate OSA symptoms. Although pharmacotherapy for the management of OSA is available, evidence on their efficacy is not robust. As such, CPAP continues to be the first-line treatment, even in patients with psychiatric comorbidity. However, more controlled studies are required, particularly to determine CPAP compliance in patients with mental illness, the impact of treating OSA on psychiatric symptoms, and the impact of the use of psychotropic medications on OSA symptoms.

Disclosure

The authors report no conflicts of interests in this work.

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