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The Complex Relationship Between Poor Sleep Quality and Chronic Obstructive Pulmonary Disease

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Abstract: Sleep-related symptoms are prevalent among patients with chronic obstructive pulmonary disease (COPD). The disease process often manifests with nocturnal respiratory symptoms. Long-acting antimuscarinic medications improve nocturnal COPD symptoms, though their effect on sleep quality requires further investigation. Those with COPD often suffer from comorbidities that negatively impact sleep, including obstructive sleep apnea (OSA) and mood disorders such as anxiety and depression. Sleep quality is also predictive of COPD exacerbations. Patients with concurrent COPD and OSA suffer from overlap syndrome (OVS), characterized by a synergistic effect on poor health outcomes. The intersection of COPD and OSA offers the clinical pulmonary audience a useful lens for ongoing basic, clinical, and translational research. Patients with OVS experience higher mortality compared with either COPD or OSA alone. This observation is attributable to the compound effect each condition has on adverse cardiovascular events. A complex interplay exists between COPD, sleep symptoms, and OSA. COPD appears to influence important non-anatomical contributors to OSA. The presence of underlying COPD makes the definitive diagnosis of OSA a challenge. Chronic non-invasive ventilation (NIV) is the backbone of therapy for OVS, OSA, and hypercarbic COPD. NIV is additionally a well-established treatment for acute COPD exacerbations and emerging research demonstrates that NIV decreases mortality and hospitalizations in patients with hypercarbic COPD. Clinicians often need to individualize therapeutic interventions for patients with COPD, OSA, and OVS, balancing the benefits and adverse effects of such interventions. NIV can have unwanted impact on the quality of life for some patients with COPD. Certain medications used for COPD, such as corticosteroids, have adverse effects on sleep quality. Future therapeutic approaches are needed to improve the sleep symptoms and health outcomes of patients suffering from COPD and OVS.

Key Words: COPD, OSA, sleep-disordered breathing, overlap syndrome

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BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common condition thought to affect ~10% of individuals over the age of 40 years.¹ The tobacco epidemic causes many cases of COPD in developed countries. Indoor and outdoor air pollution is a major worldwide source of global disease burden.^{2,3} Treatment of COPD is primarily supportive as sparse data exist regarding therapies with proven mortality benefit. Thus, efforts

to improve daytime symptoms are often the primary focus in clinical management.

Patients with COPD commonly complain of sleep disturbances. In fact, we have recently observed that >50% of patients with COPD have some complaint of sleep disturbance or daytime sleepiness.^{4,5} In recent studies of patients with moderate to severe COPD, approximately two-thirds of patients had evidence of sleep-disordered breathing (SDB).^{5,6} There is also evidence that suggests poor sleep may be a predictor of COPD exacerbations.⁷

In this review, we summarize the clinical data regarding the potential links between sleep symptoms, SDB, and COPD. The goal is to inform the general pulmonary clinician of therapeutic approaches and comanagement.

COPD: AN OVERVIEW

COPD is classically categorized into 2 phenotypic groups: patients who are primarily “pink puffers” (emphysema) versus “blue bloaters” (chronic bronchitis with productive cough). Clinically, the disease exists on a spectrum, and many patients with COPD exhibit features of both conditions.³ The underlying pathophysiology of both phenotypes lies in chronic exposure to noxious inhaled stimuli. Cigarette smoke is the most common cause of COPD in developed countries, whereas airborne pollutants, notably biomass fuels, are the major drivers of the global burden of disease. Dysregulated inflammation is among the consequences of these exposures. In emphysema, there is evidence that matrix metalloproteinases (MMP) are the key mediators of this inflammation and contribute to disease progression both by destruction of the alveolar wall matrix and through modulating inflammatory cell function. There has been particular focus on several MMP enzymes including MMP 9, 10, 12, and 28, and these proteins could serve as future therapeutic targets.^{8,9}

The robust progress in elucidating the pathophysiology of COPD is tempered by modest progress in effective therapeutics for clinical management.¹⁰ Inhaled beta agonists and antimuscarinics represent the backbone of COPD management. Inhaled steroids also play a role in some patients, although in general the benefits are fairly modest. Advances aimed at preventing exacerbations, include use of roflumilast and azithromycin, do not substantially benefit the majority of patients. Recent guidelines in COPD treatment prioritize patient-centered outcomes, such as decreasing exacerbations, and symptom-directed therapy. Although outside the scope of the current review, the confluence of asthma and COPD provides additional therapeutic targets. Daytime symptoms are often amenable to intervention whereas parenchymal lung disease may be clinically irreversible.¹¹

CURRENT VIEWS ON SLEEP DISORDERS

Sleep disorders impact daytime symptoms and quality of life of patients with various comorbidities, including COPD. The prevalence of sleep disorders is staggering. Obstructive sleep apnea (OSA) is estimated to affect up to 1 billion people

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worldwide.¹² Conservative estimates from the United States suggest that at least 30 million US adults suffer from clinically significant OSA.¹³ Despite these figures, the majority of disease remains undiagnosed and untreated.¹⁴ OSA prevalence appears to increase with severity of COPD. Several population-based studies have demonstrated a prevalence of OSA in mild COPD comparable to the general population.¹⁵ In contrast, studies of those with severe COPD suggest a high prevalence of OSA (up to 67% in 1 study). The reason for this discrepancy likely relates to the underlying severity of lung disease.¹⁵ The nature of the oxyhemoglobin curve makes patients with parenchymal lung disease prone to desaturation if their baseline saturations are below normal.¹⁶ Consequently, it remains an ongoing discussion whether OSA is simply easier to diagnose in people with severe COPD or whether severe COPD is indeed a risk factor for OSA. Mechanistic research is ongoing, and current data do not suggest a major difference in the pathogenesis of OSA in patients with COPD compared with those without COPD.¹⁷ Sleep clearly increases airway resistance in individuals with and without COPD. Ultimately, outcome-based studies are required to define the optimal metrics for disease severity. Nocturnal desaturations may be deleterious regardless of the underlying cause.^{18,19}

THE INFLUENCE OF COPD ON SLEEP QUALITY AND SYMPTOMS

Although many patients with COPD suffer from daytime fatigue and other potentially sleep-related symptoms, the influence of COPD on sleep symptoms remains understudied. Underlying sleep apnea and overlap syndrome (OVS) provide 1 explanation for this finding, although many patients have complaints in the absence of clinical sleep apnea. Studies have evaluated sleep symptoms in large epidemiological cohorts without finding consistent abnormalities. Notably, sleep symptoms are predictive of COPD exacerbations and represent an overlooked therapeutic target, discussed further below. Nocturnal COPD symptoms are a hallmark of poorly controlled COPD and contribute to interrupted sleep.

COPD is associated with poor sleep quality independent of respiratory issues. Soler and colleagues have recently reported that ~58% of COPD patients report poor sleep quality on the Pittsburgh sleep quality index (PSQI). Following a program of pulmonary rehabilitation, sleep quality improved by 19% along with concomitant improvement in dyspnea, exercise tolerance and self-efficacy, and health-related quality of life. The mechanism underlying the observed abnormalities is unclear, but medications (eg, glucocorticoids) can sometimes contribute to disrupted sleep. Sleep disorders such as sleep apnea and hypoventilation additionally contribute to sleep disturbance. Recent data suggest that treatment of the underlying airflow obstruction with tiotropium can lead to reduced nocturnal awakenings and reduced need for respiratory medications overnight. Use of acclidinium and other antimuscarinics can lead to improved sleep quality (including increased rapid eye movement sleep) and improvements in nocturnal hypoxemia.²⁰ Another mechanism of sleep disturbance in COPD relates to depression. Early morning awakening is a classic symptom of depression. It must be considered in patients with COPD who are at risk of affective disorders. Some data also support incident depression with untreated insomnia, emphasizing the importance of addressing respiratory and nonrespiratory sleep issues for the complete management of COPD. Other sleep disorders such as restless legs syndrome, periodic limb movement disorder, and parasomnias can also occur, although they

are not strongly associated with COPD per se. Nonetheless, we advocate for a thorough history and physical examination including sleep assessment in the evaluation of COPD patients.

POOR SLEEP QUALITY MAY PREDICT COPD EXACERBATION

A body of evidence supports a link between poor sleep quality and poor outcomes among patients with COPD. In a prospective analysis, the CanCOLD study (Canadian Cohort of Obstructive Lung Disease) has shown that poor sleep quality, measured by way of PSQI, was associated with a higher risk of COPD exacerbation over an 18-month period.⁷ This finding raises the possibility of targeting sleep symptoms to guide pre-emptive treatment of COPD. Sleep assessments may be clinically helpful for a number of reasons and across an array of patients with chronic pulmonary disease, though this concept requires further study. This approach could include targeting sleep symptoms to decrease the incidence of exacerbation in patients with COPD. Sleep symptoms may also define a therapeutic target for intervention in patients with end-stage lung disease for improved quality of life through restful sleep. Treatment of sleep apnea may even reduce deterioration in lung function by limiting the oxidative stress of intermittent hypoxia and reoxygenation. Targeting oxidative stress pathways may theoretically slow the progression of cardiovascular comorbidities in these patients.

PHARMACOTHERAPY OF COPD AND ITS INFLUENCE ON SLEEP

Treatment recommendations for COPD are beyond the scope of this review, but a number of considerations are important to understand how various therapies may impact sleep (Fig. 1). Certain COPD treatments directed at daytime symptoms have side effects, which worsen sleep quality, including corticosteroids and theophylline. Conversely, there is emerging evidence that treatment with longer-acting therapies such as long-acting antimuscarinics may improve nocturnal hypoxemia. Several points warrant further discussion.

First, tiotropium impacts nocturnal desaturations whether it is given in the morning or at night. These findings are not reproducible with shorter-acting agents that wear off overnight. Although sleep quality is not changed consistently with tiotropium, improvement in nocturnal hypoxemia is predicted to have benefits both for daytime symptoms and overall health. Second, glucocorticoids are frequently provided to COPD patients both during acute exacerbations and for longer-term use. Steroids have anti-inflammatory effects in COPD management. The overall benefits of these agents must be weighed against their risks. Steroids are associated with various sleep disorders including insomnia. Long-term use leads to fat deposition that predisposes patients to OSA.²¹ Theophylline highlights another unintended effect of COPD management on sleep quality. It is associated with insomnia, sleep disruption, and gastroesophageal reflux disease. In North America the drug has fallen out of clinical use due to its narrow therapeutic window, but it continues to be used in other parts of the world. The related xanthine doxofylline has been studied as a safer alternative.²²

KEY POINTS REGARDING HYPERCAPNIC COPD

Patients with COPD and hypercapnia represent a subgroup with particular relevance to the management of sleep disturbances, OSA, and COPD.

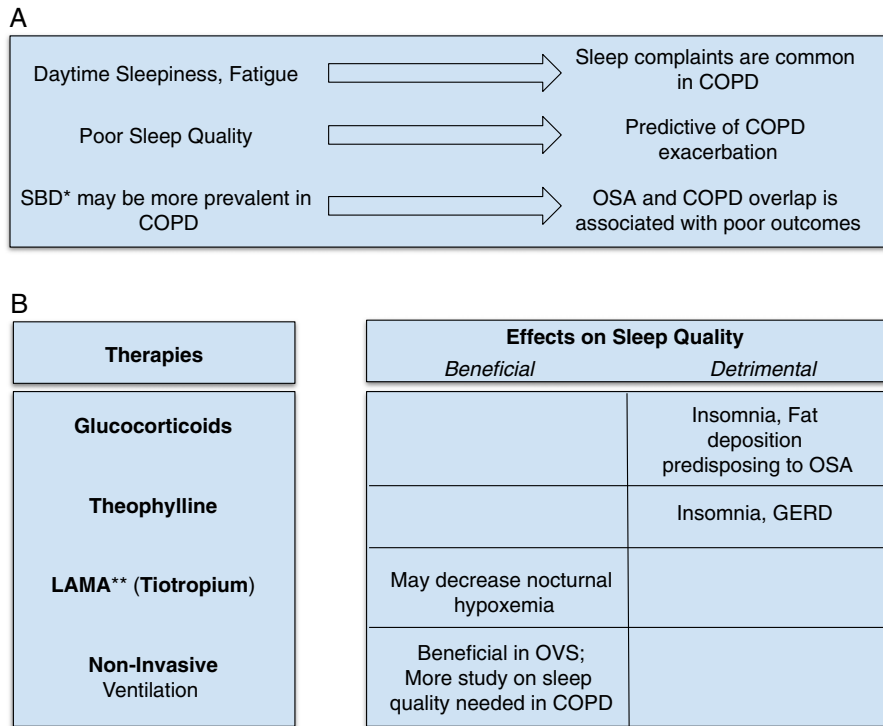


FIGURE 1. A, There are important relationships between sleep quality and COPD. B, Many COPD therapies exert an effect on sleep quality. COPD indicates chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; GERD, gastroesophageal reflux disease; NIV, noninvasive ventilation; OSA, obstructive sleep apnea; OVS, overlap syndrome. *Sleep-disordered breathing. **Long-acting antimuscarinic.

The use of noninvasive ventilation (NIV) in the management of acute COPD exacerbations is well established. In aggregate, the data strongly support the impact of NIV in these patients to prevent intubation and complications from mechanical ventilation. The potential effects on sleep disturbance is unclear. The use of NIV for the management of stable COPD is controversial and several studies have examined the subject. Despite multiple clinical studies, no clear message has emerged regarding optimal management. In one study, quality of life was actually worse for patients prescribed NIV compared with those who received usual care.²³⁻²⁵

NIV has also been studied as an intervention in patients with COPD and hypercapnia.²⁶ By lowering PaCO₂ to at least 20% from baseline, the authors observed an improvement in survival compared with usual care. The potential impact of OSA in these findings remains unclear as sleep symptoms and sleep studies were not systematically reported. Although the mechanism remains unclear, these findings indicate that lowering CO₂ helps relieve sequelae of abnormal gas exchange such as pulmonary vasoconstriction and right ventricular (RV) strain.

Another randomized trial in a related population²⁷ examined the use of NIV in patients with COPD complicated by frequent exacerbations and persistent hypercapnia. The addition of home NIV (median inspiratory pressure of 24 cm of H₂O and mean expiratory pressure of 4 cm of H₂O) compared with home oxygen alone significantly increased the time to hospital readmission or death. The use of NIV for the chronic management of COPD with hypercapnia provides a survival benefit. In practice, these potential benefits exist in the context of other patient-centered outcomes such as quality of life. Resources such as pulmonary rehabilitation programs remain a key component in improving COPD outcomes, and pulmonary rehabilitation has been shown to improve sleep quality by the PSQI.

COPD AND OSA INFLUENCE SHARED COMORBIDITIES

OSA and COPD share many major comorbidities. The association is particularly strong in cardiovascular disease, including myocardial infarction, systolic and diastolic heart failure, atrial arrhythmia, and pulmonary hypertension (PH).^{28,29} These shared associations especially impact patients with OVS, who are at increased risk of adverse cardiovascular events and overall mortality. There is mounting evidence of a synergistic effect of OSA and COPD on cardiovascular outcomes. One study³⁰ examined this issue using prospectively collected data from >10,000 participants in the Canadian Respiratory Research Network. The investigators calculated hazard ratios for a composite cardiovascular outcome (including hospitalization for myocardial infarction, cerebrovascular accident, congestive heart failure, cardiac revascularization, or all-cause mortality) in 4 groups with an Apnea-Hypopnea index (AHI) greater than or less than 30 and with or without COPD. The group with COPD and an untreated AHI > 30/hour had a statistically significant hazard ratio >2 for the composite outcome. Calculation of Relative Excess Risk due to Interaction (RERI) revealed a synergistic effect in women. Although this finding was not demonstrated in the overall population or in other subgroups, synergistic worsening of cardiovascular outcomes in OVS remains a real possibility.

A CLOSER LOOK AT THE OVS OF COPD AND OSA

COPD and OSA share many overlapping clinical features and coexist in a significant population of patients (Fig. 2). Patients with a combination of COPD and OSA are often labeled as having the OVS.³¹ OVS comprises a heterogeneous

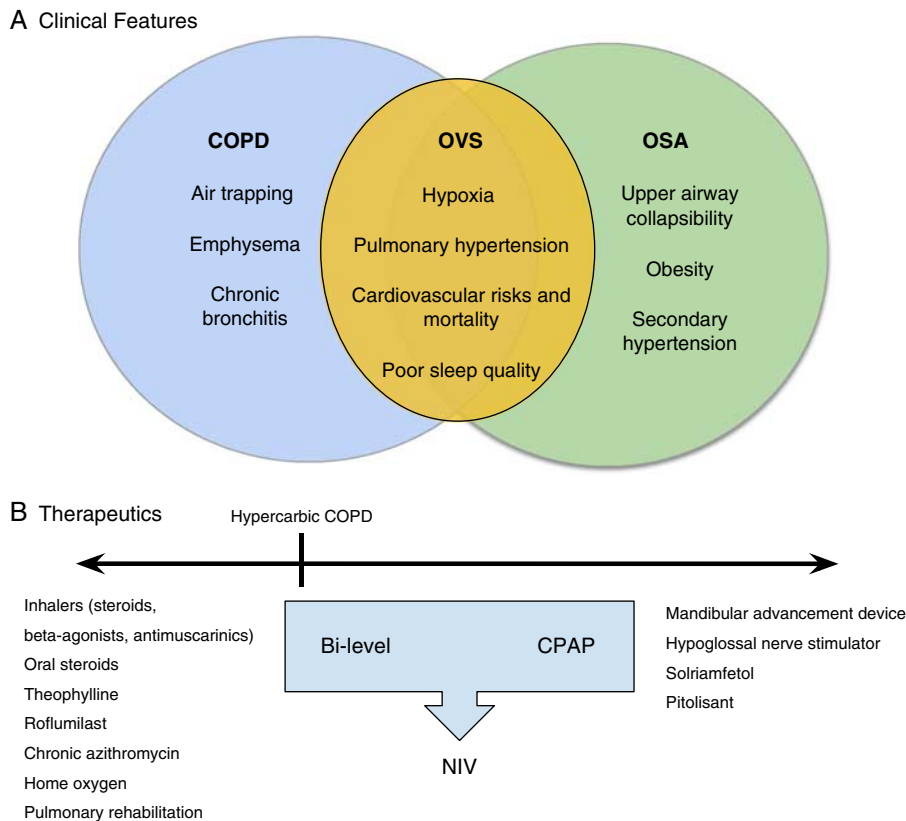


FIGURE 2. A, COPD and OSA share overlapping clinical features. These features are not mutually exclusive. B, There are distinct therapeutic options in COPD and OSA, but noninvasive ventilation has a role in both hypercarbic COPD and overlap syndrome. COPD indicates chronic obstructive pulmonary disease; LAMA, long-acting anti-muscarinic; OSA, obstructive sleep apnea; OVS, overlap syndrome; SBD, sleep-disordered breathing.

group of patients. Patients may exhibit severe COPD and mild OSA, mild COPD and severe OSA, or a true mixture of both diseases. Further work is needed to establish the optimal therapeutic approach in these patients.³²

Here several points deserve emphasis. First, OVS has been associated with worse prognosis than either disease alone, and continuous positive airway pressure (CPAP) appears to have beneficial effects on outcomes. An observational cohort study demonstrated increased mortality and higher risk of hospitalization due to COPD exacerbation in patients with OVS compared with similar patients with COPD alone.³³ Treatment with CPAP is associated with improved mortality and decreased hospitalization. A large observational study of CPAP use in patients with OVS³⁴ indicated a dose-dependent improvement in survival. The more hours per night that patients used their CPAP, the more likely they were to experience improved survival.^{33,34} Notably, neither of these studies represented a randomized controlled trial, and the data fall short of proving causation.

In OVS, the mass of the right ventricle is markedly increased compared with matched individuals with COPD alone. Specifically, OVS defined as a COPD of GOLD stage 2 or higher and OSA with AHI > 10/hour is associated with a greater degree of RV remodeling than COPD alone as measured by cardiac magnetic resonance imaging.^{35,36} A combination of parenchymal lung disease coupled with hypoxia and hypercapnia likely contributes to an increased ventricular afterload. Hypoxemia also drives myocardial fibrosis that occurs in

COPD.³⁷ These data provide insights into why the leading cause of death in COPD is cardiovascular disease. To our knowledge, there are no randomized controlled trials regarding optimal management of OVS. A number of studies have examined interventions in OSA or COPD alone, but patients most likely to benefit from intervention—patients with OVS who are at highest risk of death—have been excluded from randomized controlled trials. Further research is needed in this area.

There is a complex interplay between the pathogenesis of OSA and COPD in patients with both disorders. OSA has multiple predisposing factors that are either anatomic or non-anatomic. Upper airway collapsibility is a key anatomic feature of OSA, and arousability in response to respiratory variation is a major nonanatomic contributor.³⁸ COPD is hypothesized to influence important nonanatomic contributors to OSA and thus influence the pathophysiology of OVS. One study of 15 patients with OVS and 15 matched controls with OSA alone performed polysomnography and overnight physiological studies in both groups and found no significant differences in OSA-related traits between the groups.¹⁷ A nonstatistically significant trend toward decreased arousability in the OVS group was noted. In addition, in patients with evidence of air trapping on pulmonary function testing, there was an associated decrease in upper airway response. Patients with more severe airway obstruction demonstrated a higher loop gain with larger changes in tidal volume in response to apneic events. The authors hypothesized this latter finding to be the result of a

strong ventilatory drive secondary to hypercarbia and hypoxemia in combination with neuroplasticity-mediated increases in respiratory control center sensitivity due to chronic hypoxemia. Overall, COPD is a clear risk factor for SDB. Both the pathophysiology of OVS and the optimal clinical approach to those with OSA and severe airway obstruction and air trapping remain areas of active research.

GROUP 3 PULMONARY HYPERTENSION

The World Health Organization (WHO) classification for PH is based on the underlying etiology. WHO group 3 PH includes patients with underlying parenchymal lung disease and patients with sleep apnea and OVS. At present there are no proven therapies for WHO group 3 PH, and interventional studies with pulmonary vasodilators have not generally been effective. Nonetheless, OVS may represent an important therapeutic target as the improvements in gas exchange observed with the treatment of OVS may be beneficial in reducing RV stress. For example, the lowering of PaCO₂ and prevention of repetitive hypoxemia should reduce pulmonary vasoconstriction and therefore decrease pulmonary arterial pressure (PAP) in afflicted patients. Nocturnal hypoxemia has been noted in many forms of PH (regardless of the WHO group) and represents an underexplored therapeutic target in these patients.

MANAGEMENT OF OSA WITH CPAP AND OTHER METHODS

CPAP was developed in the 1980s and has become the standard of care for the treatment of OSA.³⁹ It overcomes the anatomic pressure exerted by soft tissue in the upper airway to maintain airway patency during sleep. Numerous studies have demonstrated its efficacy in treating the cardinal symptoms of OSA, decreasing snoring, apneic events, and daytime sleepiness. Adherence to CPAP even decreases frequency of motor vehicle accidents and improves sleep quality of bed partners of patients with OSA.

CPAP use also decreases the severity of numerous common comorbidities of OSA. Secondary analysis of the randomized controlled RICCADSA trial demonstrated decreased severity of depression after 3 months of CPAP use in patients with depression and nonsleepy OSA.⁴⁰ Multiple trials have also shown a modest improvement in hypertension (both in systolic and diastolic blood pressure) with CPAP use. Observational data suggest a decrease in adverse cardiovascular events in patients with OSA using CPAP. However, this association remains under investigation and has not been borne out in all studies. For example, the SAVE trial did not show significantly different rates of cardiovascular death, myocardial infarction, and stroke in participants with moderate-to-severe OSA treated with CPAP compared with sham-CPAP with usual care.⁴¹ Further randomized trials are underway examining this topic. Data also suggest that CPAP is associated with improvement in left ventricular ejection fraction in patients with OSA and heart failure with reduced systolic function and in left ventricular diastolic dimension in patients with both OSA and heart failure with preserved ejection fraction. In all, CPAP has proved to be a beneficial therapy in a multifactorial manner, and its efficacy for novel indications remains under investigation.

Alternative and adjunct treatments to CPAP deserve mention. These include mandibular advancement devices, pharmacotherapy targeted at sleepiness symptoms, and hypoglossal nerve stimulation. Hypoglossal nerve stimulation is among the promising new alternative therapies and was approved in 2014 by the FDA for patients with OSA refractory

to or intolerant of PAP.⁴² Specific pharmacotherapies under investigation to target residual sleepiness in OSA include the selective dopamine and norepinephrine reuptake inhibitor solriamfetol and the histamine H₃ receptor inverse agonist pitolisant.⁴³ A randomized controlled trial has recently shown that pitolisant compared with placebo decreases daytime sleepiness without an increase in adverse events in a population of patients nonadherent to CPAP therapy.³⁰ However, the mechanisms underlying residual sleepiness in OSA require further delineation, as does the effect of wakefulness-promoting medications in overall outcomes in OSA.

TREATMENT OF ACUTE AND CHRONIC HYPERCAPNIC COPD WITH BI-LEVEL POSITIVE AIRWAY PRESSURE

Bi-level positive airway pressure is a first line therapy for acute hypercapnic respiratory failure secondary to COPD exacerbation. Bi-level positive airway pressure reduces mortality and decreases the need for endotracheal intubation. A systematic review of 17 clinical trials comparing bi-level NIV to usual care in acute hypercapnic respiratory failure (defined as a pH <7.35 and a pCO₂ >45 mm Hg) demonstrated that these benefits exist both in severe hypercapnic respiratory failure (pH <7.30) and more mild cases.⁴⁴ This finding held true regardless of whether care took place in the intensive care unit or the hospital wards.

Bi-level ventilation has also been investigated as a therapy for COPD with chronic hypercapnia. In particular, it has been used as a tool in select populations in COPD, those with daytime hypercapnia and nocturnal hypoxia. As discussed above, when applied to this population, there is evidence that bi-level NIV decreases mortality.²⁶

UNANSWERED CLINICAL QUESTIONS

Despite considerable progress, a number of questions remain unanswered. First, the optimal pharmacotherapy for COPD patients to improve sleep quality and clinical outcomes remains unclear. In practice, some degree of individualization of pharmacotherapy is required. Second, we must continue to explore whether there are robust predictors of COPD exacerbations which are amenable to intervention.⁴⁵ The observation that poor sleep is a harbinger of COPD exacerbations leads to the possibility that intervening on sleep issues can prevent exacerbations.⁷ Another possibility is that sleep issues are an early marker of impending COPD exacerbation, offering hope for future interventions to prevent emergency department visits and hospitalizations. Given the expansion in machine learning, wearables, and other smart technology, novel methods may predict COPD exacerbations before patients progress to respiratory failure. Third, the optimal intervention for patients with hypercapnic COPD who are at high cardiovascular risk remains an open question. Do all of these patients need sleep studies or other forms of nocturnal assessment? The role of bi-level PAP in OVS also remains unproven, and robust clinical trials are needed to assess hard outcomes and define optimal therapy. Answers to these questions would allow clinicians to prioritize interventions. Only through further basic, clinical, and translational research will new therapeutic targets emerge.

CONCLUSIONS

Many factors contribute to poor sleep quality in COPD. The clinical interplay between COPD and OSA is multifaceted and affects a large patient population. Patients with COPD are

frequently troubled by sleep-related symptoms that may or may not be causally related to OSA. Factors such as nocturnal respiratory symptoms and comorbidities such as mood disorders play key roles. The exact prevalence of OVS remains under investigation, partially because of the diagnostic subtleties of studying OSA in a population predisposed at baseline to oxygen desaturation. What is clear is that patients with severe COPD and OSA have worse outcomes than patients with either condition alone. NIV provides a survival benefit for these patients and for patients with COPD and hypercapnia generally. These conditions share many comorbidities including systemic and PH and cardiovascular disease.

The overlap of COPD and OSA will remain a rich area for basic physiological and clinical research. Such work promises to yield benefits in patient-centered outcomes such as quality of life, an invaluable prize in the setting of chronic parenchymal lung diseases, such as emphysema, which lack therapies to reverse the underlying pathology. It also remains possible that directly targeting sleep symptoms in chronic pulmonary diseases, including COPD, will improve other key outcomes such as frequency of COPD exacerbations. Tiotropium reduces nocturnal COPD symptoms and acclidinium may benefit sleep quality. The treatment of one condition has important implications for the other. Steroids contribute to insomnia and disrupt sleep generally, whereas NIV adversely impacts quality of life measures in certain COPD patients. Clinicians must consider such realities as they craft individualized treatment plans for patients. Future research will aid the optimal therapies for patients with COPD who suffer from poor sleep quality.

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