REVIEW ARTICLES

JCSM
Journal of Clinical Sleep Medicine

pii: jc-00080-14
http://dx.doi.org/10.5664/jcsm.4540

Sleep Disorders in Chronic Obstructive Pulmonary Disease: Etiology, Impact, and Management

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality and may frequently be complicated by sleep disorders. Insomnia and obstructive sleep apnea are commonly encountered in patients with COPD. Nocturnal hypoxemia is also prevalent in COPD may occur despite adequate awake oxygenation and can be especially severe in rapid eye movement sleep. Additionally, several factors—some of them unique to COPD—can contribute to sleep-related hypoventilation. Recognition of hypoventilation can be vital as supplemental oxygen therapy itself can acutely worsen hypoventilation and lead to disastrous consequences. Finally, accruing data establish an association between restless leg syndrome and COPD—an association that may be driven by hypoxemia and/or hypercapnia. Comorbid sleep disorders portend worse sleep quality, diminished quality of life, and multifarious other adverse consequences. The awareness and knowledge regarding sleep comorbidities in COPD has continued to evolve over past many years. There are still several lacunae, however, in our understanding of the etiologies, impact, and therapies of sleep disorders, specifically in patients with COPD. This review summarizes the latest concepts in prevalence, pathogenesis, diagnosis, and management of diverse sleep disorders in COPD.

Keywords: COPD, insomnia, obstructive sleep apnea, restless legs syndrome, hypoventilation

Citation: Budhiraja R, Siddiqi TA, Quan SF. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J Clin Sleep Med* 2015;11(3):259–270.

That sleep is adversely affected in chronic obstructive pulmonary disease (COPD) has been long recognized.[1] COPD affects 5% to 10% of the adult population in the United States and is a major contributor to global disease burden.[2] The prevalence of insomnia symptoms, insomnia disorder, restless leg syndrome, and hypoxemia is increased in COPD.[3–5] Furthermore, polysomnographic (PSG) evaluation generally reveals decreased sleep efficiency and lower mean overnight oxygen saturation in COPD patients compared to controls.[6]

In COPD, the pathogenesis of sleep disorders appears to be a complex and multifactorial process, likely consequent to one or more of the following: physiological changes associated with sleep, hypoxemia, hypercapnia, inflammation, COPD medications, and/or nicotine use. Comorbid disorders as well as primary sleep disturbances may also contribute to disrupted sleep in COPD patients. For example, nocturnal gastroesophageal reflux (GERD) is associated with both symptoms of sleep apnea and COPD, and may contribute to the pathogenesis, and concomitant occurrence of both disorders.[7] GERD may also influence sleep quality which could potentially contribute to some of the sleep complaints reported by persons with COPD.[8] The following sections describe the diverse sleep disorders and sleep-related abnormalities encountered in patients with COPD.

INSOMNIA

Epidemiology

Insomnia is defined as difficulty falling asleep, staying asleep, waking up too early, or having unrefreshing sleep. The prevalence of insomnia is increased in patients with COPD.[6] One study found that DSM-IV insomnia was reported in 32.9% of those with COPD, compared with only 20.3% of those without COPD.[3] A history of COPD was associated with significantly increased odds of insomnia 1.9 (1.5–2.5) after adjusting for age and gender ($p < 0.001$). PSG did not reveal a significant overall difference in sleep latency or sleep efficiency in those with or without COPD. However, a higher proportion of persons with COPD had a low sleep efficiency (< 82%) than those without COPD (44% vs. 31%, $p = 0.04$). A recent study found a high prevalence of insomnia disorder (27.3%), defined as presence of insomnia symptoms along with daytime manifestations, in patients with COPD.[4]

Whether COPD severity is related to worse sleep is unclear. Some studies suggest worse sleep in more severe COPD,[9] while other studies have not shown an association between FEV1 and reported sleep quality.[4,10] Associated respiratory symptoms such as cough and sputum production appear to be better predictors of sleep disturbances.[1,10,11] However, in one

Table 1—Possible etiologies of insomnia in patients with COPD.

- Respiratory symptoms including cough, sputum production and dyspnea
- Nicotine use
- Nicotine withdrawal
- Increased work of breathing
- Hypoxia
- Increased Sympathetic Activity
- Comorbid anxiety and depression
- Comorbid sleep disorders including SDB and RLS
- Use of medications such as theophylline

study, severity of dyspnea using the Medical Research Council dyspnea scale did not correlate with prevalence of insomnia.[4] The authors hypothesized that nocturnal dyspnea may have a different etiology than diurnal dyspnea. While the latter may be related to exertion and inability to do tasks due to shortness of breath, several other factors, such as nocturnal hypoxemia and associated increased pulmonary vascular pressures, may contribute to nocturnal dyspnea.

Etiology

An insight into the etiology of insomnia in COPD may be vital in devising therapeutic strategies. Several factors may plausibly contribute to these sleep disturbances (**Table 1**).[4] COPD can be associated with disabling dyspnea. Dyspnea may be worse supine and while in bed attempting to sleep (*vide supra*). Hypoxemia may contribute to nocturnal dyspnea and sleep disturbances. Indeed, oxygen use was found in one study to be associated with lower odds of insomnia.[4] Minimum oxygen saturation was an independent predictor for a high score on a psychiatric sleep symptom scale in another study.[6] However, data on the role of oxygen in improving sleep in COPD have been conflicting. While some studies demonstrate a salutary effect of supplemental oxygen,[4,12,13] others do not.[9,14] Nocturnal dyspnea may also be attributable to the asthma/bronchitic phenotype of obstructive lung disease. Medications used for COPD, especially β-agonists, have also been suggested to contribute to insomnia. However, a recent study did not show an adverse influence of any inhalers on sleep.[4] In fact, univariate analyses revealed lower insomnia prevalence in patients on β-agonist inhalers, although the effects were not statistically significant in multivariate analyses. Inhaled steroids are commonly used in COPD, but their effect on sleep has not been systematically assessed. Smoking has been associated with sleep disturbances in several studies,[4] sympathetic activation from nicotine being one possible culprit. However, acute nicotine withdrawal when asleep may also be responsible for disturbed sleep. Furthermore, restless legs syndrome (RLS) may be encountered more frequently in obstructive lung disorders than in healthy controls (*vide infra*) and may contribute to insomnia. RLS symptoms worsen during COPD exacerbations, further affecting sleep.[15]

Psychiatric disorders such as depression and anxiety frequently accompany chronic medical disorders. Prevalence rates of up to 80% for depression and 74% for anxiety have been reported in COPD patients.[16,17] In one study, over 20% of patients with COPD reported using an antidepressant.[18] Depression in COPD is independently associated with lower quality of life.[19] Anxiety and depression can precipitate or worsen insomnia. Furthermore, the association between psychiatric disorders and insomnia is likely bidirectional.[3] Insomniacs have a significantly higher likelihood of reporting one or more psychiatric disorders compared with those with no sleep complaints.[20]

Hyperarousal appears to be a feature of primary insomnia.[21,22] Some studies have shown increased sleeping heart rate in insomniacs.[23,24] Insomniacs have higher ACTH and cortisol secretion,[25] metabolic rate,[26] and global cerebral glucose metabolism during sleep and awake[27] compared with normal controls. Several factors in COPD may alter the sympathovagal balance with a resultant increase in sympathetic activity. Chronic hypoxia may contribute to sympathetic activation.[28–31] Hypercapnia has been shown to increase sympathetic activity in some studies.[32–34] COPD is associated with systemic inflammation[35,36] and oxidative stress,[37,38] which in turn, also augment sympathetic outflow.[39–41] Impaired baroreflex responses, hyperinflation, elevated pulmonary artery pressures, dyspnea, physical inactivity, pronounced swings in intrathoracic pressure, and medications can all contribute to autonomic dysfunction.[42–44] Indeed, COPD patients have increased muscle sympathetic nerve activity, which decreases with short term oxygen supplementation.[45] Plasma norepinephrine levels are elevated in hypoxemic patients with COPD, and levels decrease with long-term oxygen therapy.[46] Patients with COPD also demonstrate depressed heart rate variability in association with systemic inflammation and lung function impairment.[47,48] Use of noninvasive positive-pressure ventilation improves heart rate variability in acute COPD exacerbation.[49] Furthermore, six weeks of therapy with tiotropium suppresses the exercise-induced increase in sympathetic activity in COPD patients.[50] It is possible that the synergistic effects of sympathetic activation in COPD and insomnia may contribute to some of the adverse outcomes seen in persons with COPD comorbid with insomnia.

Impact

Insomnia is associated with a decrement in quality of life. Presence of COPD augurs a further deterioration in health-related quality of life.[4] Self-reported sleep quality is also worse in COPD patients with insomnia compared to COPD patients without insomnia.[4] COPD patients with insomnia, compared to those without insomnia, are more likely to suffer from daytime sleepiness.[4] This may potentially lead to decreased productivity at work, absenteeism, and traffic accidents.

Insomnia is associated with a gamut of adverse outcomes. As a caveat, information regarding several of these outcomes comes from studies in the general population or patients seen in sleep clinics rather than specifically from patients with COPD. Odds of prevalent[51] and incident[52] hypertension are increased in insomnia with objective short sleep duration. Insomnia with < 6 hours nightly sleep duration is associated with increased odds of diabetes.[53] Insomnia symptoms alone are also associated with high hemoglobin A1c levels.[54] Insomnia

with short sleep duration is also associated with neuropsychological deficits including slower processing speed and increased visual memory errors and omissions.[55] Both insomnia and short sleep duration (≤ 5 hours) were independently associated with atherosclerosis risk, as determined by ultrasonographic measurements of carotid intima-media thickness, in a study of 86 elderly volunteers (age ≥ 65 years).[56] Risk of acute myocardial infarction is increased in a dose-dependent manner in persons with symptoms of insomnia.[57] The Penn State Cohort data showed four-fold increased odds of mortality in insomniacs who slept less than 6 hours compared to the those with no insomnia and normal sleep duration.[58] Analyses of data from the Finnish Twin Cohort showed a significant association between self-reported poor sleep and risk of mortality, especially in those with somatic disease (presumably including COPD).[59] It is possible that insomnia may contribute to increased incidence of these adverse outcomes in patients with COPD. Indeed, one study followed 98 adults with spirometrically confirmed COPD for a median of 2.4 years and found that insomnia symptoms at baseline predicted increased COPD exacerbations and worse survival during follow-up.[10]

Evaluation and Management

Insomnia is primarily a clinical diagnosis. Patients should be asked about the duration, frequency, and severity of their sleep symptoms.[60] The course and precipitants of the symptoms, and relationship to the symptoms of the lung disorder (cough, sputum production, dyspnea) should be assessed. Inquiries should be made regarding daytime habits that might contribute to insomnia (e.g., nicotine use, alcohol, and caffeine intake), sleep hygiene and possible daytime consequences of sleep problems, including fatigue, sleepiness, and quality of life.[61] Patients should also be asked about any other disorders that could contribute to insomnia.[3] Physical exam should be targeted towards assessing comorbidities. Sleep logs can help provide relatively objective evidence of presence and course of sleep disturbance. Scales such as the Insomnia Severity Index can help quantify the severity of insomnia at baseline as well as provide objective evidence of improvement with therapies. Actigraphy is largely limited to the research arena, but may be used clinically if history is not clearly indicative of type or severity of sleep problems. Several interventions improve sleep quality in COPD patients. Optimal treatment of COPD to minimize symptoms such as cough, secretions, and dyspnea will likely lead to better sleep quality. Smoking cessation should be strongly encouraged. Organic sleep disorders including RLS and sleep disordered breathing (SDB) should be optimally treated. Oxygen may theoretically have several salutary effects on sleep in COPD (**Table 2**). Larger studies are needed to assess effects of long-term oxygen supplementation on sleep in these patients.

Cognitive behavioral therapy for insomnia (CBT-I) is an effective therapy in primary insomnia and appears to be superior to sedatives in the long term.[62,63] CBT-I also appears to be beneficial in insomnia comorbid with cancer, human immunodeficiency virus infection, chronic pain, psychiatric disorders such as depression.[63,64] A small study suggests feasibility and efficacy of performing CBT-I in COPD patients.[65] In view of the potential adverse effects of pharmacotherapy in COPD, larger trials need to be conducted assessing CBT in COPD. Other interventions, such as stimulus control therapy alone, may also be beneficial.[63]

Table 2—Potential beneficial effects of oxygen on sleep and breathing in COPD.

- Decreases minute ventilation, preventing auto-PEEP
- Alleviates nocturnal hypoxemia-associated arousals
- Decreases pulmonary artery pressures
- Alleviates anxiety and depression
- Attenuates sympathetic activity

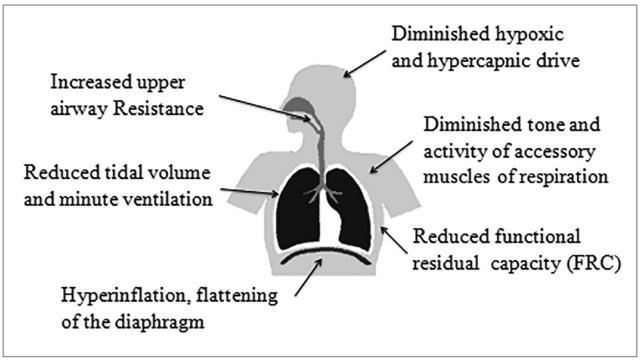
Therapy of attendant anxiety and depression may help improve sleep. One randomized, controlled trial reported significant improvements not only in depressive symptoms after CBT, but also improved sleep efficiency at 8-month follow-up in patients with COPD and depression.[66]

Despite concerns regarding their respiratory depressant effects, benzodiazepines have been assessed for treatment of insomnia in COPD.[67] Medications may be required to improve sleep when nonpharmacologic measures prove inadequate. One week of temazepam 10 mg therapy in 14 patients with stable, severe, normocapnic COPD did not cause a significant increase in carbon dioxide tension during sleep or worsen dyspnea or sleepiness.[68] However, decrease in minute ventilation, worsening of diaphragmatic endurance and decrease in oxygen saturations have been reported with traditional benzodiazepines, suggesting need for caution.[67] Furthermore, tolerance, dependence, cognitive impairment, and abnormal sleep-related behaviors are concerns with both benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists.[61]

Melatonin can also improve sleep quality in COPD.[69] Use of the MT(1)/MT(2) melatonin receptor agonist ramelteon 8 mg for one night in 25 subjects (≥ 40 years) with moderate to severe COPD resulted in a significant increase in total sleep and sleep efficiency without causing respiratory depression or worse hypoxemia.[70] The likelihood of cognitive impairment and abuse liability is also lower than that with benzodiazepine receptor agonists. However, more clinical trials need to be done to assess the effects of ramelteon on diverse physiological and polysomnographic parameters in persons with COPD.

Doxepin is a histamine-1 receptor antagonist that has been shown to alleviate psychophysiological insomnia.[71] The sleep promoting effect is seen primarily at low doses (3 mg or 6 mg), in contrast to the higher doses (10 mg or more) required for antidepressant action. However, efficacy of other antihistaminic agents in insomnia has not been demonstrated consistently.[72] Furthermore, these agents can be limited by their anticholinergic adverse effects which include precipitating narrow angle glaucoma or urinary retention. Trazodone is commonly used for insomnia. However, its efficacy, especially in the long-term is not clear. Mirtazapine binds to 5-HT_{2A} and 5-HT_{2C} in addition to the H_1 receptor and may have a role in promoting weight gain apart from its effects on sleep. Thus, it may have a potential role in a subset of COPD patients where both these benefits would be desirable. Nevertheless, it needs to be reiterated that these agents have not been systematically evaluated in COPD. Finally,

Figure 1—Factors contributing to hypoxemia during sleep in patients with COPD.



it is plausible that antioxidants[73] and anti-inflammatory agents,[36] if proven effective, may improve sleep by improving the symptoms of COPD as well as decreasing sympathetic activity.

SLEEP-RELATED HYPOXEMIA

Epidemiology

Isolated hypoxemia (desaturation in absence of primary sleep disorders such as obstructive sleep apnea) during sleep is a common occurrence in patients with advanced COPD, and may occur despite adequate awake oxygenation. Indeed, significant nocturnal hypoxemia has been reported in up to 70% of COPD patients with daytime saturations between 90% and 95%.[74,75] Daytime oxygen saturation, however, is highly predictive of nocturnal desaturation. Owing to the mechanisms detailed below, desaturations are more frequent and more pronounced during REM sleep.

Medicare criteria to qualify for nocturnal oxygen include an arterial $PO_2 \leq 55$ mm Hg or an arterial oxygen saturation $\leq 88\%$, for at least 5 minutes taken during sleep. A decrease in arterial $PO_2 > 10$ mm Hg or a decrease in arterial oxygen saturation > 5% for at least 5 minutes during sleep, associated with symptoms or signs reasonably attributable to hypoxemia (e.g., cor pulmonale, "P" pulmonale on EKG, documented pulmonary hypertension, and erythrocytosis), can qualify for nocturnal oxygen therapy per Medicare guidelines as well. It should be mentioned that there can be a significant variation among physicians in the interpretation of nocturnal oximetry.[76]

Etiology

Several mechanisms contribute to a nocturnal decrease in oxygen levels in COPD (**Figure 1**). Alveolar hypoventilation leading to decreased minute ventilation may be the primary mechanism of nocturnal hypoxemia. Minute ventilation can drop approximately 16% during NREM sleep and 32% during REM sleep in patients with COPD.[77] During wakefulness, respiration is not only under metabolic control, but also influenced by voluntary processes such as speaking and swallowing. During sleep, chemoreceptors and ventilatory centers become the sole controllers of respiration. Levels of PaO_2, $PaCO_2$, and pH influence the respiratory pattern. As a result, PaO_2 can decrease by 3–10 mm Hg and $PaCO_2$ can increase by 2–8 mm Hg. In persons with high oxygen reserve, this may portend only a slight drop in oxygen saturations. Limited oxygen reserves, however, as suggested by daytime saturations of 93% or below, may correspond to the steep portion of oxyhemoglobin dissociation curve (which describes the relationship between PO_2 and oxygen saturations), whereby a slight drop in PaO_2 culminates in pronounced oxygen desaturation. Hence, daytime oxygen saturation is among the strongest predictors of nocturnal desaturation in patients with COPD.[78] In those with similar daytime oxygenation, COPD patients with daytime hypercapnia have worse nocturnal hypoxemia than those without daytime hypercapnia.[79]

Impact

Acute episodes of nocturnal desaturation can cause elevation in systemic systolic and mean pulmonary artery blood pressures.[80] These repetitive and transient desaturations over time can lead to chronic pulmonary hypertension in patients with OSA.[81] However, it is not clear if nocturnal hypoxemia in patients with COPD alone leads to development of right ventricular dysfunction or cor pulmonale. Cardiac arrhythmias have also been linked with nocturnal desaturations[82] and may contribute to the higher than expected nocturnal death rate in COPD patients.[83] Finally, nocturnal hypoxemia may be associated with arousals, and leads to sleep fragmentation.[84] COPD patients with nocturnal hypoxemia have a lower survival rate than those without nocturnal hypoxemia, with oxygen therapy associated with a trend towards increased survival.[85]

Evaluation and Management

Patients with COPD with relatively low daytime saturation (< 93%) may be considered for overnight oximetry. However, PSG should be considered in those with symptoms suggestive of sleep disordered breathing (*vide infra*). A cyclical (sawtooth) pattern on overnight oximetry suggests sleep disordered breathing and may also merit a PSG.[86]

Supplemental oxygen is indicated in those who meet the Medicare criteria detailed above. In the landmark Nocturnal Oxygen Therapy Trial, continuous supplemental oxygen therapy was associated with lower mortality compared to only nocturnal therapy.[87] Similarly, a Medical Research Council Trial from UK found improved mortality benefits of oxygen therapy used for 15 hours/day including sleep in comparison to no supplemental oxygen.[88] However, the role of oxygen in symptomatic patients with COPD and moderate hypoxemia at rest and desaturation with activity is less clear. National Heart, Lung, and Blood Institute Long-term Oxygen Treatment Trial is expected to provide more information regarding the role of oxygen in this subset of COPD patients.

Oxygen therapy in COPD patients produces some decrease in mean pulmonary arterial pressure, even though it may not improve pulmonary hemodynamics significantly.[89,90] Supplemental oxygen may help improve sleep quality in COPD patients with nocturnal hypoxemia.[12] However, optimal treatment of obstructive lung disease with bronchodilators can also alleviate nocturnal hypoxemia and improve sleep quality.[91–93] While oral steroids also improve total sleep time and oxygenation during sleep in stable COPD, numerous potential side

effects including insomnia make this therapy undesirable.[94] Lung volume reduction surgery decreases airflow obstruction, air-trapping, and hyperinflation, and improves sleep quality and nocturnal oxygenation.[95]

SLEEP HYPOVENTILATION

Epidemiology

As detailed above, some degree of hypoventilation and increase in $PaCO_2$ from wake to sleep is physiologic. Sleep-related hypoventilation refers to a greater than normal increase in $PaCO_2$ during sleep. It is defined as an increase in the $PaCO_2$ to > 55 mm Hg for ≥ 10 minutes, or an increase in the $PaCO_2$ by ≥ 10 mm Hg above the awake supine value to a value over 50 mm Hg for ≥ 10 minutes[96] Due to difficulty in monitoring $PaCO_2$ during sleep, data regarding sleep-related hypoventilation in COPD are limited. In one study of 54 stable hypercapnic COPD patients without concomitant sleep apnea or morbid obesity, 43% were found to have sleep hypoventilation.[97] BMI, baseline $PaCO_2$, and time spent in REM sleep were the strongest predictors of the severity of sleep hypoventilation. In contrast, another study of 23 COPD patients, most of whom did not have daytime hypercapnia, showed a mean increase in transcutaneous PCO_2 during sleep of only 6 mmHg, similar to that in controls.[98]

AASM guidelines propose that end-tidal pCO_2 ($PETCO_2$) or transcutaneous PCO_2 ($tcPCO_2$) may be used as surrogates of arterial $PaCO_2$ for diagnostic PSG and transcutaneous PCO_2 for titration PSG. In a comparative study, however, neither $PETCO_2$ nor $tcPCO_2$ were a consistently accurate reflection of $PaCO_2$.[99] Another comparative study of anesthetized adult patients revealed that $PETCO_2$ had a large negative bias and $tcPCO_2$ has a small positive bias compared to $PaCO_2$.[100] Hence, there are limitations in using noninvasive monitoring of CO_2 in diagnostic studies, especially in patients with COPD. Indeed, AASM guidelines advise using clinical judgment when assessing the accuracy of $PETCO_2$ or $tcPCO_2$ readings, especially when the values do not fit the clinical picture.[99]

Etiology

Sleep-related hypoventilation results from an exaggerated increase in $PaCO_2$ from wake to sleep owing to mechanisms detailed above, including diminished ventilatory drive, increased upper airway resistance and mechanical disadvantages imposed by hyperinflation. Daytime hypercapnia, which can be seen in severe COPD as a result of significant decline in alveolar ventilation, is a strong predictor for sleep hypoventilation. A recurrent increase in nocturnal $PaCO_2$ can plausibly lead to bicarbonate retention and blunting of the ventilatory responsiveness, which could in turn worsen daytime hypercapnia. Obesity causes loading of respiratory muscles and increased upper airway resistance, and is associated with blunted chemosensitivity. Hence, BMI is another predictor of sleep hypoventilation in several studies. Sleep apnea events, especially when frequent, can also contribute to the nocturnal increase in $PaCO_2$.

Supplemental oxygen therapy, an integral therapy for patients with COPD and hypoxemia, itself can worsen hypoventilation. In one study of 80 clinically stable COPD patients with hypercapnic respiratory failure, 21% developed nocturnal hypoventilation after a night of supplemental oxygen therapy.[101] BMI and daytime oxygenation were the best predictors for development of nocturnal hypoventilation. Similarly another study showed that use of an additional liter of oxygen over the daytime flow rate (as recommended by the American Thoracic Society/European Respiratory Society guidelines) in COPD patients with chronic hypercapnic respiratory failure improved nocturnal oxygenation, but was associated with greater hypercapnia and acidosis the next morning.[102]

Impact

Hypercapnia in COPD patients is a poor prognostic indicator.[103] It decreases myocardial and diaphragmatic contractility, increases pulmonary artery pressure and predisposes to arrhythmias. Sleep-related hypoventilation is associated with a reduced life expectancy.[104] One study showed significantly greater improvement in sleep duration with oxygen plus nasal pressure support ventilation compared to oxygen alone, suggesting that hypoventilation may be a stronger determinant of sleep quality than nocturnal hypoxemia alone.[105]

Evaluation and Management

Morning headaches in patients with COPD may suggest nocturnal hypoventilation and CO_2 retention. If nocturnal CO_2 retention is suspected, CO_2 monitoring should be considered along with the PSG. While serial $PaCO_2$ determination, usually with an indwelling arterial catheter, is the gold standard for diagnosing sleep hypoventilation, it is invasive and is not practical outside of research studies. Surrogate measures of $PaCO_2$, such as transcutaneous CO_2 or end-tidal PCO_2 monitoring can be used, but are not routinely performed during standard PSG. Moreover, the reliability and validity of these surrogates, especially in severe COPD, may be limited.

Medicare guidelines allow for nocturnal intermittent positive pressure ventilation (NIPPV) use in stable hypercapnic patients if daytime $PaCO_2$ is ≥ 45 mm Hg and nocturnal oximetry reveals saturations ≤ 88% for at least 5 consecutive minutes not caused by obstructive upper airway events.[106] Despite strong data favoring use of NIPPV in COPD patients with acute hypercapnia, studies assessing NIPPV use in chronic hypoventilation have shown conflicting results. A meta-analysis of 4 randomized controlled trials in hypercapnic patients with stable COPD did not find a consistent effect on sleep efficiency, lung function, gas exchange, respiratory muscle strength, or exercise tolerance. However, the small sample size of these studies precluded a definite conclusion regarding effect of NIPPV in COPD patients.[107] In contrast, COPD patients treated with NIPPV along with oxygen compared to oxygen alone in one study demonstrated improved sleep quality and diminished sleep-related hypercarbia, albeit without significant effect on FEV1 or $PaCO_2$.[104] Additionally, NIPPV improved survival, but quality of life appeared to worsen in this study. More recently, controlled mode NIPPV was shown to improve diurnal $PaCO_2$, vital capacity, and mean inspiratory pressure.[108] Another study showed improvement in awake $PaCO_2$ with use of nocturnal NIPPV in COPD.[105]

High intensity NIPPV (high pressure and high back-up rate) improves gas exchange and mortality in stable hypercapnic

Table 3—Plausible factors that may lead to a higher than chance concurrence of COPD and OSA.

COPD Features that may Contribute to Increased Prevalence and Symptoms of OSA

1. Chronic oral steroid use causing increased neck size
2. Increased upper airway edema from cor pulmonale
3. Decreased exercise capacity contributing to obesity
4. Muscle weakness leading to easy upper airway collapsibility

OSA Features that may Contribute to Increased Prevalence and Symptoms of COPD

1. Systemic inflammation contributing to lower airway inflammation
2. Ischemia-reperfusion injury and oxidative stress
3. Worse gastrointestinal reflux from negative intrathoracic pressure, potentially worsening the lung disease
4. Nasal congestion from PAP therapy contributing to breathing problems
5. Poor sleep contributing to daytime sleepiness and mood disturbances, which could contribute to smoking
6. Worsening of asthmatic component of COPD

Conditions that may Increase Risk of Prevalence or Symptoms of both COPD and OSA

1. Gastroesophageal reflux disease
2. Allergic rhinitis
3. Obesity
4. Smoking

COPD patients.[109] It has been proposed that the high pressure component of high intensity ventilation is actually responsible for these therapeutic improvements.[110] If used, it should be ensured that respiratory support is sufficient to alleviate hypoventilation and hypercarbia. Unfortunately, tolerability and adherence may be an issue with higher pressures.

Average volume assured pressure support (AVAPS, Philips Respironics) and intelligent volume assured pressure support (iVAPS, ResMed) are newer hybrid modes that use proprietary algorithms to calculate the pressure support needed to achieve a target tidal volume or alveolar ventilation, respectively. iVAPS has been compared with high intensity NIPPV in a recent randomized crossover study.[111] In stable chronic hypercapnic COPD patients, iVAPS showed a greater decrease in nocturnal hypercapnia and a trend towards more restful sleep at 6 weeks of treatment.

OBSTRUCTIVE SLEEP APNEA

Epidemiology

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary (COPD) are both common pulmonary disorders. OSA may be present in ~10% to 30% in persons with COPD, which is similar to its prevalence in the general population.[112–114] Concurrence of OSA and COPD is termed "overlap syndrome" and occurs in approximately 1% of adults in the general population.[115]

Etiology

The coexistence of two common disorders, COPD and OSA, may likely just be a chance occurrence.[115] However, several factors might actually predict a higher concurrence rate than merely by chance (**Table 3**). Some patients with severe COPD are on chronic oral steroids (or high dose of inhaled steroids), which may contribute to central obesity and fat deposition in neck, increasing the risk of OSA. Severe COPD may lead to elevated pulmonary pressures, right ventricular dysfunction and right heart failure (cor pulmonale). This may lead to edema in the pharyngeal soft tissues, predisposing to OSA. A decrease in exercise capacity may contribute to obesity, a prominent risk factor for OSA. COPD is also associated with generalized muscle weakness, which could portend higher upper airway collapsibility.

Conversely, several mechanisms can be hypothesized whereby OSA could contribute to development and symptoms of COPD. OSA can lead to both local and systemic inflammation. Snoring related vibrations are postulated to cause soft tissue damage and local inflammation.[116] OSA is associated with higher levels of inflammatory mediators such as interleukin 6 (IL-6), C reactive protein (CRP), intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and tumor necrosis factor alpha (TNF-α).[117] Breath condensates of OSA patients have increased IL-6 and 8-isoprostane levels, suggesting bronchial airway inflammation.[118] An overexpression of IL-8 in human bronchial epithelial cells has been demonstrated in response to a vibratory stimulus, similar to what may be seen in OSA.[119] Inflammation can not only reduce the airway lumen, but it can potentially lead to alveolar wall destruction, which may be an important factor in development of COPD. Indeed, higher levels of IL-6, IL-8, CRP, and TNF-α are seen in patients with COPD.[120] Furthermore, hypoxia from OSA can cause upregulation of xanthine oxidoreductase in pulmonary endothelial cells,[121] similar to that produced by tobacco smoke,[122] which could contribute to the pathogenesis of COPD. Additional factors mentioned in **Table 3** may potentially lead to increased presence and/or severity of COPD in patients with OSA. OSA can worsen gastrointestinal reflux and PAP therapy can worsen nasal inflammation, both of which can worsen the asthmatic component of COPD and dyspnea.

Finally, several conditions contribute to both COPD and OSA and could lead to a higher than expected concurrence of the two. GERD may have a bidirectional relationship with OSA, and has also been shown to worsen the asthmatic component of COPD. Acid reflux into airways in turn can cause increased airway reactivity by either local inflammation or by enhancing vagal tone.[123] It is plausible that nocturnal GERD may play a role in the development of obstructive lung disease and OSA symptoms. Indeed, a recent study showed worse respiratory and sleep apnea symptoms in those with GERD.[7] Allergic rhinitis and nasal polyps may cause nasal obstruction and contribute to sleep-disordered breathing.[124] Allergic rhinitis has been linked to asthma and chronic bronchitis as well,[125] and could act as a potential link between COPD and OSA. Obesity is a major risk factor for OSA and has been associated with a higher incidence and severity of asthma. Asthma is more difficult to control with coexistent obesity and OSA.[126] Weight reduction has been shown to improve severity of OSA and control of asthma.[127] However, similar correlations between COPD and OSA are yet to be evaluated. Finally, smoking, the major risk factor for COPD,

may also contribute to an increased prevalence and severity of OSA.[128]

Both OSA and COPD are associated with inflammatory cell activation and hypoxia.[113] These may lead to endothelial dysfunction, and consequently several adverse outcomes.[113] However, data comparing endothelial dysfunction in COPD with comorbid OSA versus either alone are lacking.

Impact

COPD comorbid with OSA is associated with more pronounced hypoxemia and hypercapnia and adverse clinical outcomes compared with COPD or OSA alone.[129] The concurrence of these two is associated with more cardiac dysrhythmias[130] and portends more severe pulmonary hypertension and right heart failure.[131] In one case series, pulmonary hypertension was observed in 86% of those with COPD comorbid with OSA (n = 17) compared to only 16% of patients with OSA but no COPD (n = 67).[132] The incidence of right heart failure in comorbid COPD and OSA was 12% in another case series, and was associated with lower mean nocturnal oxygen saturation, lower awake PaO_2, and higher $PaCO_2$.[133]

COPD comorbid with OSA is associated with higher mortality compared to either disease alone.[134] In a large study of 10,981 men, presence of COPD conferred a 7-fold increase in all-cause mortality in patients with OSA.[135] A prospective study with median follow-up of 9.4 years also demonstrated higher mortality when untreated comorbid OSA was present than with COPD alone.[136] The causes of death were primarily cardiovascular (28.1%), cancer (26%), and pulmonary (25.8%). The study also showed a higher prevalence of severe COPD exacerbation requiring hospitalization when OSA was present in COPD patients. However, in CPAP treated patients with COPD and OSA, the risk of mortality and severe exacerbations was similar to that observed in patients with COPD only. Furthermore, degree of positive airway pressure adherence appears to affect outcomes. In an observational large cohort of COPD comorbid with OSA patients, greater time on CPAP was associated with reduced mortality.[137]

Evaluation and Management

COPD patients with symptoms suggestive of OSA, such as snoring or witnessed apneas, should be evaluated by PSG. Additionally, in patients with COPD, presence of pulmonary hypertension out of proportion to the disease severity may indicate comorbid OSA, and PSG should be considered.[138]

While home sleep testing may be a cheaper and relatively more convenient way to diagnose sleep disordered breathing, it has not been validated in COPD and is not recommended by American Academy of Sleep Medicine.[139] In-lab PSG is superior to in-home testing due to the ability to continuously monitor oxygen saturation and noninvasively monitor PCO_2 either via $PETCO_2$ or $tcPCO_2$. For similar reasons, in-lab titration PSG may be better than auto-CPAP titration.

Continuous positive airway pressure (CPAP) therapy is the accepted standard for treatment of OSA. Apart from eliminating apneas, CPAP off-loads respiratory muscles and reduces work of breathing, which decreases hypoventilation and improves daytime oxygenation in patients with COPD.[140] CPAP can also counteract auto-PEEP, and have a mild bronchodilator effect by decreasing chronic airway edema and hyperresponsiveness.[140] Additionally, OSA may plausibly worsen COPD through diverse mechanisms (**Table 3**). Consequently, improvement in OSA with CPAP therapy may translate into a concomitant improvement in COPD.[112] Indeed, apart from the expected improvement in sleep, spirometric parameters (FEV1, FVC) and gas exchange (PaO_2, $PaCO_2$) appear to improve with CPAP treatment of patients with OSA and COPD.[141] CPAP treatment for OSA also reduces the number of COPD-related severe exacerbations and hospital admissions.[136,142] Notably, oxygen alone is not an effective treatment for this condition. In a prospective cohort of 95 patients with moderate/severe COPD (GOLD stage II-III) and moderate/severe OSA (AHI > 15), 5-year survival estimate was 71% in CPAP-treated patients compared to 26% in patients on long-term oxygen therapy alone.[143] NIPPV has not been systematically evaluated in OSA comorbid with COPD. Bilevel PAP for nocturnal noninvasive ventilation is used for persistent hypoventilation leading to hypoxemia despite resolution of obstructive events with CPAP. Similarly, the specific role of oral devices is not clear in patients with coexistent COPD and OSA. Lifestyle modifications such as weight reduction and smoking cessation may have salutary effects on both these disorders, and should be strongly encouraged. Finally, treatment of underlying pathophysiology of obstructive lung disease may improve upper airway collapse. In a single-arm pilot study, upper airway collapsibility as measured by passive critical closing pressure (Pcrit) significantly improved after using orally inhaled fluticasone propionate for 16 weeks.[144]

CENTRAL SLEEP APNEA

There is a dearth of studies assessing prevalence of central sleep disordered breathing in patients with COPD. COPD is associated with several comorbidities or complications, which in turn can be associated with central sleep apnea or Cheyne-Stokes respiration. For example, patients with severe COPD can develop pulmonary hypertension and right ventricular dysfunction. One case series of 38 patients with pulmonary hypertension from different etiologies revealed Cheyne-Stokes respiration in 39% of the patients.[145] Similarly, COPD is frequently associated with left ventricle diastolic dysfunction[146] as well as systolic heart failure,[147] both conditions known to be associated with Cheyne-Stokes respiration.

RESTLESS LEGS SYNDROME

Epidemiology

Restless legs syndrome (RLS) is a common sensorimotor disorder. It is characterized by the following four International Restless Legs Syndrome Study Group (IRLSSG) criteria: (1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, (2) The urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying or sitting, (3) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and (4) The urge to move

or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.[148] The urge to move is primarily reported in the legs, but arms and trunk may also be involved. Furthermore, in severe cases, symptoms may last all day, but a history of some worsening towards the end of the day may frequently be elicited.

RLS is present in 2% to 15% of the general population.[149–151] It is more common in women and prevalence increases with age.[149] A history of RLS in first-degree relatives is offered in majority of patients with RLS, and close to 80% of persons with RLS have periodic limb movements of sleep.[152] However, whether these features are true for RLS comorbid with COPD is not known.

The prevalence of RLS is higher in persons with COPD than those without COPD.[153] One study showed significantly higher odds of incidence of RLS in those with self-reported obstructive airway disease than those without obstructive airway disease (OR = 2.8).[5]

Etiology

While the etiology of RLS in COPD is yet to be clearly elucidated, hypoxemia and/or hypercapnia may contribute to the pathogenesis of RLS. Indeed, a higher prevalence of RLS has been reported in other pulmonary disorders including sarcoidosis and pulmonary hypertension. Hypoxia, through the hypoxia inducible factor-1 (HIF-1) pathway, may lead to an increase in tyrosine hydroxylase and vascular endothelial growth factor (VEGF). The former is a rate limiting enzyme in dopamine synthesis and is increased in RLS. VEGF expression is increased in the substantia nigra and in the anterior tibialis muscles of those suffering from RLS. Alterations in nigrostriatal and/or extrastriatal dopaminergic pathways may be seen in persons with RLS. Nicotine, the primary risk factor for COPD, exerts some effects through stimulation of dopaminergic pathways. Whether these are related, and could influence the association between COPD and RLS is unclear. Iron deficiency is likely causally related to RLS.[154] Low ferritin in some COPD patients may be responsible for RLS. Similarly, comorbid renal failure may underlie RLS in some patients. Several medications including antidepressants and dopamine antagonists can worsen restless legs syndrome symptoms.[155] Finally, some individuals may be genetically predisposed to develop RLS.[156]

Impact

RLS is associated with diminished quality of life.[149,150,157] RLS patients usually have difficulty falling and staying asleep,[158,159] and PSG demonstrates lower sleep efficiency and longer adjusted mean sleep latency and higher arousal index.[160,161] The risk of depression, anxiety, and panic disorder is also increased in persons with RLS.[162,163] RLS may also contribute to cardiovascular disease, although data assessing this association are conflicting.[164,165]

Evaluation and Management

Diagnosis of RLS is based on a typical history and does not need a PSG for confirmation. PSG may, however, be considered if history suggests sleep disordered breathing or another sleep disorder that would warrant this testing. It should be noted several conditions can mimic RLS and should be excluded prior to making this diagnosis.[166] These include, but are not limited to, cramps, positional discomfort, arthritis, and neuropathy.

No specific studies have been conducted to assess the therapy of RLS specifically in COPD patients. Dopaminergic drugs should be the mainstay of RLS therapy in patients with COPD, as in those without this disorder.[167] Levodopa is shorter acting (onset of action 10–15 minutes, half-life ~ 1 hour) and has a higher risk of augmentation, especially at higher doses and with longer treatment duration. Hence it is not an optimal therapy for chronic use. It may, however, be used on as needed basis in case of infrequent symptoms. Pramipexole (half-life 8–12 hours) and ropinirole (half-life 5–6 hours) are effective for long-term treatment of RLS.[168,169] Common side-effects of dopamine receptor agonists include nausea, dizziness, tiredness, headache, insomnia, and dry mouth.[169] Excessive daytime sleepiness can occur at higher doses but is less common at the doses used for RLS. Pathological gambling and hypersexuality are other less commonly reported side effects.[170] It has been suggested that dopamine agonists may potentially have salutary effects on symptoms such as cough and mucus secretion frequently seen in persons with advanced COPD.[171] If borne out, this may be an additional benefit for persons with COPD and RLS. On the other hand, some studies suggest a suppressive effect of dopamine agonists on ventilatory responses to hypoxemia and hypercapnia via dopamine-mediated inhibition of carotid body chemoreceptors.[172] This indicates a need for caution, and close follow-up after medication initiation, especially in persons with severe COPD with hypoxemia and/or hypercapnia.

A number of studies have shown that several other agents including alpha2-delta calcium channel ligands (e.g., gabapentin, pregabalin) are effective in the treatment of RLS.[173] For example, gabapentin has been used in idiopathic RLS[174] and RLS comorbid with renal failure,[175] and may be a potentially useful drug in RLS comorbid with COPD. It can be especially useful when pain is the predominant manifestation of RLS. Opiates and benzodiazepines have been used to treat idiopathic RLS with varying efficacy.[167] Opioids reduce dyspnea in patients with advanced COPD[176] and may ameliorate comorbid RLS in such patients. However, possibility of respiratory depression may limit their use, especially in hypercarbic patients. Similarly, safety of benzodiazepines has not clearly been established in COPD.

A randomized, controlled trial showed efficacy of oral iron replacement in ameliorating symptoms in RLS patients with low-normal serum ferritin levels (15–75 ng/mL).[177] Iron deficiency, if present, should be treated with an aim of keeping ferritin above 75 ng/mL.

Factors which may aggravate RLS symptoms should be avoided. These include use of nicotine, caffeine, and alcohol; and medications including selective serotonin reuptake inhibitors (SSRI) such as escitalopram and fluoxetine, other antidepressants including mianserin and mirtazapine, antipsychotics such as olanzapine, and L-thyroxine.[155] Lifestyle modifications including exercise,[178] sleep hygiene, massage, and warm water baths, may help ameliorate the symptoms.[179] Other therapies including acupuncture,[180] pneumatic compression devices,[181] and near infrared light[182] have been evaluated for RLS in small studies.

CONCLUSION

COPD is frequently associated with sleep-related abnormalities as well as primary sleep disorders. Presence of these comorbidities may worsen the already diminished quality of life in COPD patients and increase the odds of several other adverse health outcomes including higher mortality. A regular inquiry by health providers to COPD patients regarding sleep and potential sleep disorders, followed by management as warranted, may have the potential of ameliorating these risks and improving the quality of life and survival. While emerging data provide much needed information on the etiology, impact and management of sleep disorders in COPD, much still needs to be accomplished. Future studies should attempt to understand the specific role of diverse diagnostic techniques and pharmacologic and non-pharmacologic measures in diagnosis and treatment of insomnia, sleep disordered breathing and RLS in patients with COPD.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April, 2014
Submitted in final revised form October, 2014
Accepted for publication December, 2014
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. Authors discuss potential treatments and therapies to be assessed in future, that may currently be considered off-label or investigational.