

Sleep and Sleep Disorders in Chronic Obstructive Pulmonary Disease

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Key Words

Chronic obstructive pulmonary disease · Hypoventilation · Insomnia · Pulmonary function · Sleep disturbances

Abstract

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in the US. Numerous studies have demonstrated that sleep disturbances are common in COPD patients, with more prominent complaints in patients with more severe disease and with increasing age. Sleep disturbances may occur due to the effects of breathing abnormalities on sleep and sleep disruption. However, other etiologies may include the medications used to treat COPD, comorbid anxiety and depression, and the presence of comorbid sleep disorders. The respiratory disturbances that occur in these patients during sleep have been evaluated by examining sleep-related oxygen desaturation, reduction in pulmonary function during sleep, and development of hypoventilation during rapid eye movement sleep. Treatment includes use of nocturnal oxygen therapy, noninvasive positive pressure ventilation, and long-acting medications. There has been little study on improving sleep quality beyond treating the respiratory disease, despite the fact that numerous studies show poor sleep quality, a high prevalence of insomnia, and tolerability of newer hypnotic agents in the setting of COPD. This article defines the scope of sleep problems in the setting of COPD, reviews the impact of sleep on ventilation, explores the role of obstructive sleep apnea in the setting of COPD, and reviews therapeutic options.

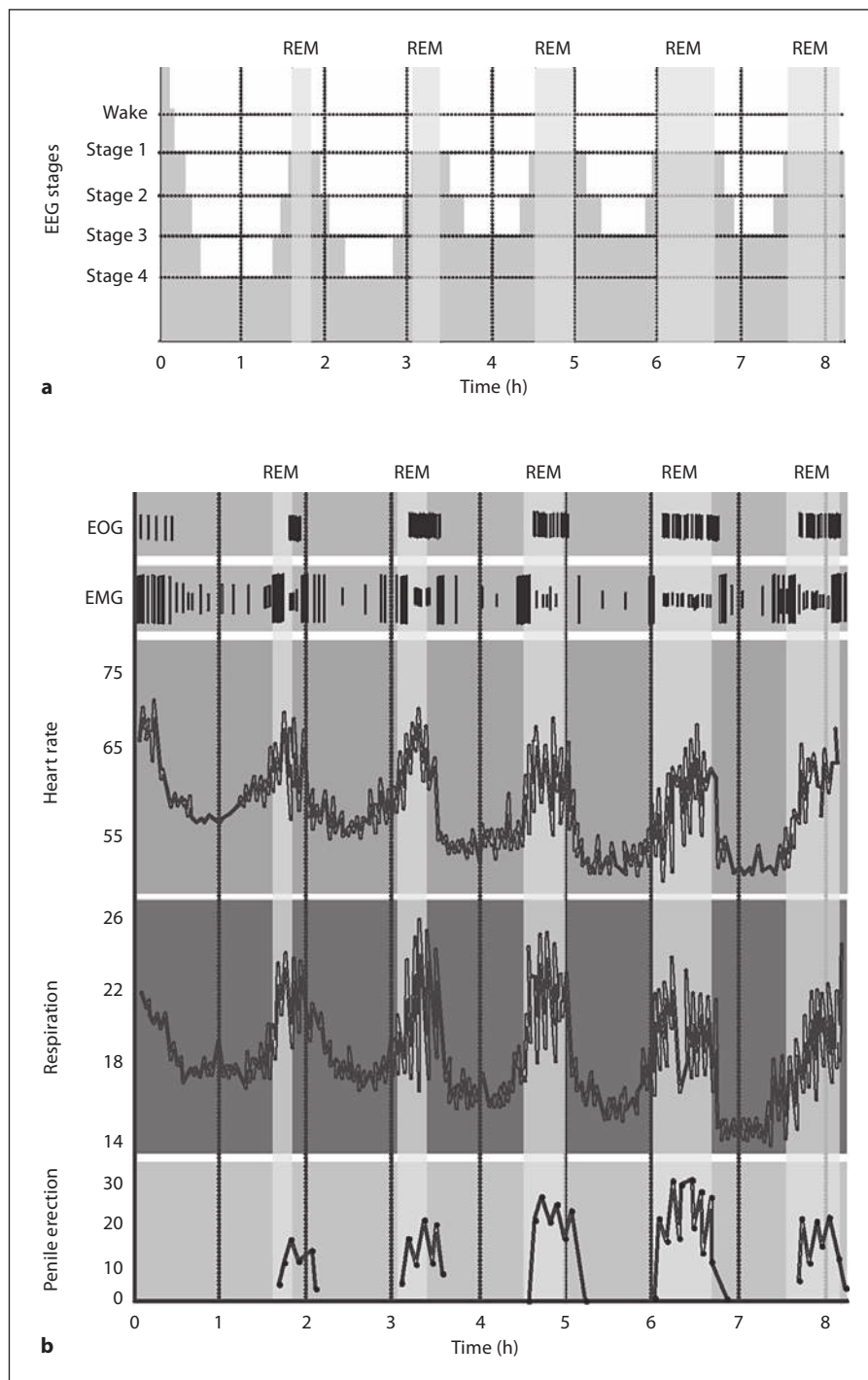
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Introduction

Until the 1950s, sleep was considered to be a single state of rest. In 1953, however, electroencephalographic (EEG) recordings revealed that sleep actually occurs in stages that differ as much from each other as sleep differs from wakefulness (fig. 1). The transitional stage from wake, called stage 1 sleep (N1), is followed by stage 2 sleep (N2), with decreased frequency of EEG waves and an increase in their amplitude, together with spike clusters referred to as sleep spindles and slow oscillation called K complexes. Stage 3 and 4 sleep (N3) is deep sleep, and the amplitude of low-frequency waves continues to increase while the number of spindles decreases (slow-wave sleep). Collectively, these sleep stages are termed non-rapid eye movement (NREM) sleep; the sequence from stage 1 to stage 4 is typically about 1 h [1].

Following a period of slow-wave sleep, however, EEG recordings show that the NREM stages of sleep transform to rapid eye movement (REM) sleep, a very active physiological state profoundly different from NREM sleep (table 1). After about 10 min in REM sleep, the brain typically cycles back through the NREM sleep stages [1]. With each cycle, the REM period becomes progressively longer. As people age, the time spent in N3 sleep decreases, but the percentage of time spent in REM sleep remains unchanged [2]. These sleep phases affect respiration in different ways.

Fig. 1. Physiological changes in a male volunteer during the various sleep states in a typical 8-hour period of sleep. **a** The duration of REM sleep increases from 10 min in the first cycle to up to 50 min in the final cycle; note that slow-wave (stage 4) sleep is attained only in the first two cycles. **b** The upper panels show the electrooculogram (EOG) and the lower panels show changes in various muscular and autonomic functions. Movement of neck muscles was measured using an electromyogram (EMG). Other than the few slow eye movements approaching stage 1 sleep, all other eye movements evident in the EOG occur in REM sleep. The greatest EMG activity occurs during the onset of sleep and just prior to awakening. The heart rate (beats per minute) and respiration (breaths per minute) slow in NREM sleep, but increase almost to the waking levels in REM sleep. Finally, penile erection occurs only during REM sleep (after Schmidt et al., 1983; source: Purves et al. [1], reproduced with permission).



Impact of Sleep on Normal Ventilation

As shown in figure 2, at sleep onset, ventilation decreases due to multiple contributing factors. The reticular activating system and metabolic rate decrease, chemo-

sensitivity is reduced, and upper airway resistance increases with sleep onset. The resulting decrease in ventilation results in an increase in the partial pressure of carbon dioxide in the arterial blood (P_{aCO_2}) despite the decrease in metabolic rate, and a decrease in the partial

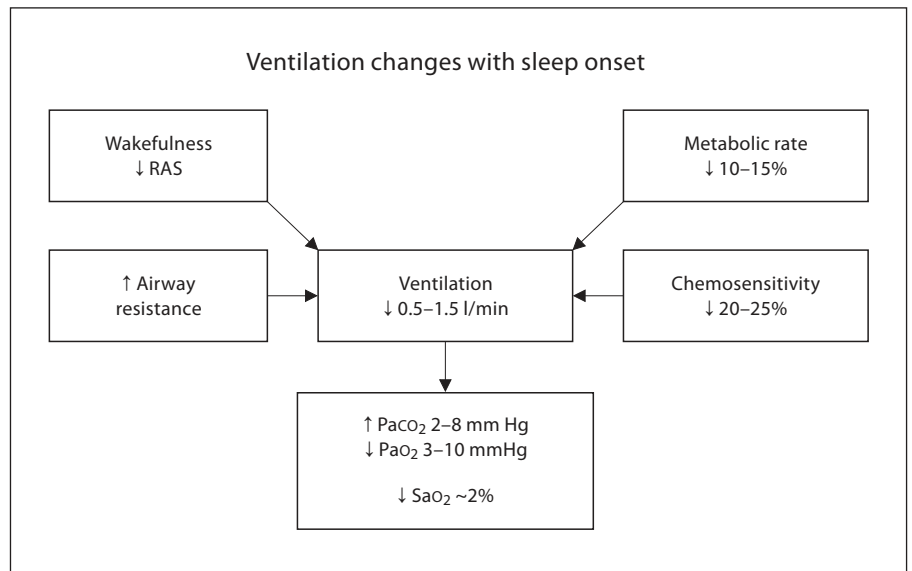


Fig. 2. In normal individuals experiencing a typical sleep cycle, decreases in reticular activating system (RAS) activity, metabolic rate, and responsiveness to arterial PaO_2 and PaCO_2 along with increased airway resistance lead to decreased ventilation and subsequent changes in arterial blood gases during sleep (source: Mohsenin [2], p 110, fig. 1, reproduced with permission).

Table 1. REM versus NREM sleep

Physiologic variable	NREM	REM
Heart rate	regular	irregular
Respiratory rate	regular	irregular
Blood pressure	regular	variable
Skeletal muscle tone	reduced	absent
Brain O_2 consumption	reduced	increased
Ventilatory response	reduced	reduced
Temperature	normal	poikilothermic
Sexual changes	rare	frequent

Adapted from Parmeggiani [76].

pressure of oxygen (PaO_2) levels despite respiration remaining stable with only rare apneas. To the contrary, REM sleep is characterized by significant breath-to-breath variability, increased mean respiratory frequency, marked reductions in ventilation with bursts of eye movements, and further decreases in the carbon dioxide response [2].

An early study of ventilation during sleep in normal subjects [3] revealed a greater decrease in ventilation in REM sleep compared to wakefulness. These falls in ventilation resulted almost entirely from changes in tidal volume (VT) and mean inspiratory flow (VT/TI) and not from changes in timing. The fractional abdominal contribution to ventilation fell during slow-wave sleep but

returned to awake levels during REM sleep, suggesting that the actual rib-cage and abdominal contributions to ventilation were equally reduced during REM sleep compared to awake periods. Despite a decrease in overall ventilation during slow-wave sleep, the ribcage contribution to ventilation was actually higher. Snoring profoundly affected the proportions of rib-cage and abdominal contributions [3]. Decreases in minute ventilation during slow-wave sleep compared to wakefulness resulted from a change in tidal volume and not from changes in respiratory frequency which remained relatively consistent during sleep.

Figure 3 illustrates the effect of carbon dioxide levels on ventilation during sleep/wake stages. It shows that during REM sleep, there is less sensitivity to hypercapnia as compared to NREM stages and wakefulness [4].

Impact of Sleep on Ventilation in Patients with Chronic Obstructive Pulmonary Disease

Two distinct clinical patterns are seen in patients with chronic obstructive pulmonary disease (COPD). Chronic bronchitic patients (type B) are hypoxemic, retain CO_2 , have cor pulmonale and a chronic productive cough, and are commonly overweight. Emphysematous patients (type A) have relatively normal arterial blood gases, are thin and hyperinflated, and have a significantly decreased lung diffusion capacity for carbon monoxide. Both type A and type B patients typically have characteristic fea-

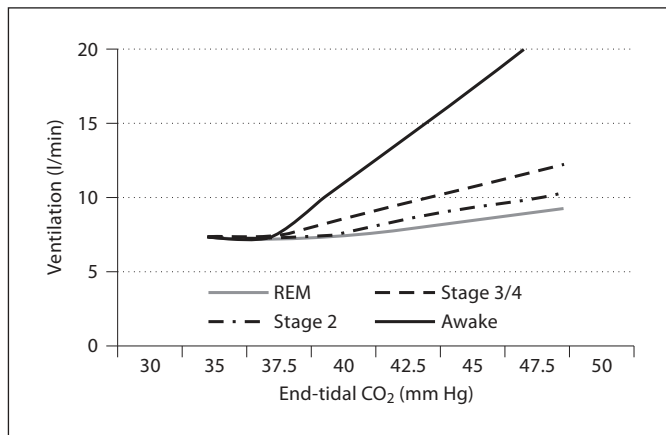


Fig. 3. The effect of increasing CO₂ levels on ventilation during wakefulness as compared to different sleep stages. During wakefulness there is a robust response to CO₂ levels manifested by a rapid escalation in minute ventilation; however with sleep, the response to CO₂ levels is reduced with the lowest responsiveness occurring during REM sleep (source: Collop et al. [74], reproduced with permission).

tures of chronic bronchitis and emphysema [5]. When 4 type B and 6 type A patients were monitored during sleep to determine the incidence of abnormal breathing and oxygen desaturation in each group [5], notable differences were observed. Type B patients demonstrated severe sleep hypoxemia attributed to lower baseline oxygen saturations during sleep, and also due to severe episodic desaturation caused by an altered breathing pattern. Conversely, type A patients experienced only minor reductions in oxygen saturation during sleep [5]. The hypoxemia reported in this study has been well documented elsewhere as occurring primarily during REM sleep [5–9] and potentially causing sustained pulmonary hypertension [10, 11]. Overall, patients who are most hypoxemic when awake experience the most severe hypoxemia when asleep [12]. COPD patients may spend more than 30% of sleep time with low oxygen levels [13].

Mechanisms of Nocturnal Deoxygenation

Various mechanisms are thought to contribute to the nocturnal hypoxemia that occurs with COPD. Table 2 lists potential mechanisms. First, it is intuitively apparent that because COPD patients have a lower oxygen saturation during wakefulness, the normal ventilation changes that occur with sleep exacerbate this preexisting state to

Table 2. Proposed mechanisms for NOD

Start lower on oxyhemoglobin dissociation curve
Reduced chemoresponsiveness (less likely to arouse from sleep due to hypoxia or hypercapnia)
More reliance on accessory muscles during wakefulness –
REM-related atonia causes loss of the activity of these muscles
Greater reduction in functional residual capacity with sleep onset
Increased upper airway resistance
Increased ventilation-perfusion mismatch

the point of severity. Second, hypoventilation that occurs at sleep onset is in part due to a reduction in muscle tone causing increased upper airway resistance. In addition, during REM sleep there is further reduction in skeletal muscle tone. This atonia is thought to be both more profound in COPD patients during REM sleep and the result of an increased reliance on intercostal and accessory muscles of inspiration during waking hours, which causes profound effects on ventilation when these muscles become atonic during REM [14]. This REM-related hypoventilation has also been observed in a wide variety of other lung, neuromuscular and skeletal disorders, due to a fall in tidal volume related to a loss of accessory muscle use [15]. Third, because COPD patients have blunted chemoresponsiveness, they arouse less frequently during sleep, and breathing patterns do not have an opportunity to normalize to the waking state, thus oxygen saturation is impaired for extended periods of time [16]. Fourth, ventilation-perfusion mismatch is thought to occur as studies have shown that there are greater changes in oxygen levels than in carbon dioxide levels during REM sleep [17–19]. This may be in part due to reduction in functional residual capacity, which decreases approximately 10% when an individual is in the recumbent position, with further evidence suggesting that patients with COPD may experience even more profound decreases [20]. The combined effect of these mechanisms is a persistent and dramatic decrease in oxygen saturation throughout the REM cycle [21, 22].

Diagnostic Criteria and Predictors

Sleep-related hypoventilation/hypoxemia due to COPD falls under the ICD-9 code 780.57. Diagnostic criteria appear rather arbitrary, but have been established as an oxygen saturation of hemoglobin (SaO₂) <90% for >5 min (nadir 85%) or >30% of total sleep time (TST) at SaO₂

<90%). In the unlikely event that it is possible to obtain a blood gas measure during sleep, a diagnostic criterion is a PaCO₂ disproportionately increased relative to wakefulness (>45 mm Hg). Nocturnal oxygen desaturation (NOD) has been associated with a variety of medical problems, including episodic pulmonary hypertension. Rodent experiments have shown that when PaO₂ is reduced intermittently during sleep, the rodents develop right ventricular hypertrophy [23, 24]. Other conditions indirectly associated with NOD include increased arrhythmias, polycythemia, and increased mortality [25]. NOD, however, is not associated with differences in quality of life, sleep quality, or daytime function [26]. Interestingly, diagnosing NOD may require more than one nocturnal oximetry as large night-to-night variations have been noted [27].

In a subset analysis of the Sleep Heart Health Study [28], data from 1,132 participants with mild COPD were reviewed to determine predictors of oxyhemoglobin desaturation during sleep. After adjusting for confounding factors, the odds ratios for experiencing >5% of TST with oxyhemoglobin saturation (SpO₂) <90% were calculated across a range of values measuring the forced expiratory volume in the 1st s and forced vital capacity (FVC). In the absence of sleep apnea, the adjusted odds ratio for nocturnal oxyhemoglobin desaturation increased at levels of FEV₁/FVC below 65%. In participants with an FEV₁/FVC of 60–65%, the adjusted odds ratio for desaturation to <90% for >5% TST was 1.92 (confidence interval: 1.1–3.34). The adjusted odds ratio conferred by an FEV₁/FVC <60% was 3.36 (confidence interval: 1.98–5.7) [28]. Thus, quite low levels of FEV₁/FVC were needed for a significant association with NOD, suggesting that patients with more serious COPD are more likely to experience this problem. Although these studies have examined physical endpoints, other opportunities for research include sleep quality, neurocognitive function, memory, and other comorbidities [29].

A number of NOD predictors have been studied. Lower pulmonary function test results (FEV₁/FVC <60%) have been associated with NOD [30], but this finding has not been found in other studies. Unlike patients with cystic fibrosis, those with COPD who experience exercise-related desaturation do not necessarily also experience NOD [31]. Earlier studies suggested inconsistent results for an association between NOD and awake SaO₂, PaO₂, or PCO₂ [12, 32]. However, more current studies do suggest that NOD is more likely in patients with COPD when daytime SaO₂ ≤93%, and unlikely when daytime SaO₂ ≥95% [31, 33, 34].

Sleep-Disordered Breathing in COPD: ‘Overlap Syndrome’

In patients with COPD, sleep apnea is not uncommon and can further exacerbate gas exchange during sleep. Known as the overlap syndrome [35], this association has been reported in 11% of 265 patients with obstructive airway disease referred to a sleep laboratory, most of whom were older males. However, the true prevalence of this syndrome is unknown [36]. These patients demonstrated lower PaO₂ and higher PaCO₂ during wakefulness, as well as higher pulmonary artery pressure and more hypoxemia during sleep compared to other study subjects. Recent data suggest that obstructive sleep apnea is not any more common in COPD than in the general population but that sleep-disordered breathing has a more severe course [37]. In a separate study, patients with sleep apnea had a lower 5 year mortality if they were heavy smokers or had COPD [38]. COPD patients at risk for overlap syndrome (those with polycythemia, cor pulmonale, or neuropsychological impairment) should be appropriately screened. Oximetry will show sawtoothing oxygen desaturation during NREM periods, with persistently low SaO₂ during REM. Treatment with continuous positive airway pressure or bilevel positive airway pressure is indicated for patients with an overlap syndrome [39].

Noninvasive Treatment Options

Nocturnal oxygen therapy (NOT) is sometimes recommended for NOD with concomitant polycythemia or cor pulmonale. Although multiple studies have examined the use of NOT in the setting of NOD [40, 41], none have demonstrated a decrease in mortality resulting from this treatment. Although risk of CO₂ retention has been a clinical concern, in fact these risks have been shown to be typically modest and nonprogressive. Some small studies suggest that patients will sleep better with NOT, but the data are not highly convincing [42, 43].

Nocturnal positive pressure ventilation (NPPV) is the delivery of mechanically assisted breaths without placement of an artificial airway, usually with the use of a fitted nasal mask. In the setting of COPD, NPPV is more controversial than its use in the setting of neuromuscular disease as study results have been discrepant. The early interest in using NPPV for patients with severe COPD was based upon physiologic studies showing that because patients with COPD were hyperinflated, they relied upon

accessory and parasternal muscles as opposed to the diaphragm during inspiration, which greatly increased the oxygen cost of breathing [44]. However, a meta-analysis of the medical literature [44] published about a decade ago showed that most studies of NPPV in stable COPD subjects showed minimal or no benefits in pulmonary function, gas exchange, or sleep efficiency. Respiratory muscle fatigue was not considered to be an important contributing factor in stable patients.

Several short-term studies (10–120 min) [45, 46] have shown some benefit. NPPV appears to decrease the inspiratory work of breathing, reduce diaphragmatic electromyogram activity, improve PaO₂, decrease PaCO₂, and increase minute ventilation. Overall, the level of evidence for use of NPPV is not strong (table 3). Studies suggest it works best in those with higher PaCO₂, but that approximately 25% of patients will be intolerant [47]. Either volume or pressure modes are equally effective, but pressure support appears to be better tolerated and more comfortable [47].

Consensus statement guidelines for NPPV in COPD [44] indicate that conflicting results of studies hinder strong evidence-based recommendations, but nonetheless suggest some clinical strategies. Those most likely to benefit are individuals with substantial daytime CO₂ retention and NOD. Indications for usage include: (a) symptoms (e.g. fatigue, dyspnea, or morning headache); (b) physiologic criteria (PaCO₂ ≥55 or 50–54 mm Hg with NOD), or (c) PaCO₂ 50–54 mm Hg with recurrent hospitalization related to episodes of hypercapnic respiratory failure. Clinical considerations related to NPPV use include patient motivation and compliance, severe cognitive dysfunction, need for continuous ventilatory assistance, financial and caregiver resources, and mask fit. Patients with severe swallowing dysfunction are not good candidates for NPPV [48].

Two studies [49, 50] that evaluated the use of long-term oxygen therapy with or without NPPV in patients with severe COPD had discrepant results. A small study [49] of patients randomized to NPPV, oxygen therapy, or a combination of the two for 2 weeks reported no difference in sleep stages, and worse sleep efficiency with NPPV. No clinical benefits were observed. A larger, long-term study [50] comparing oxygen therapy with NPPV or a combination of both reported improved PaCO₂, resting dyspnea, and health-related quality of life but no difference between treatment groups in lung function, inspiratory capacity, exercise tolerance, or sleep quality. Notably, hospital admissions and intensive care unit stays decreased dramatically in patients re-

Table 3. Levels of evidence supporting NPPV use for stable COPD (Hill [75], reproduced with permission)

Benefit	Level of evidence
Symptoms	B
Ventilation	B (short-term A)
Sleep duration	B
Respiratory mm strength	A (short term)
Functional capacity	C
During use	A
After use	none
Survival	C
Health status	B
Reduced hospitalization	C

A = Multiple randomized controlled trials; B = single randomized controlled trial; C = case series, cohort trials.

ceiving combination treatment (45 and 75%, respectively). Treatment was not associated with increased survival, however.

Drug Treatments

Two small studies have investigated the therapeutic effects of medroxyprogesterone on oxygen desaturation. The first study of 17 subjects reported increased PaO₂ and decreased PaCO₂ during wake, but no significant improvement in oxygen saturation during sleep [51]. A recent placebo-controlled crossover study conducted in 13 postmenopausal women found treatment improved SaO₂ and transcutaneous carbon dioxide tension during sleep. Changes were also noted in REM sleep, indicating a therapeutic response throughout the sleep cycle. Treatment effects persisted even following treatment cessation, suggestive of a hormonal therapeutic response that is worthy of additional study [52]. Conversely, studies of almitrine [53–55], a peripheral chemoreceptor agonist, have not demonstrated a significant therapeutic effect.

Studies of the effects of β-agonists on sleep in the setting of COPD demonstrate, in general, no adverse effects on sleep or nocturnal oxygenation [56, 57]. Studies of anticholinergics showed that ipratropium improved overall mean nocturnal SaO₂ as well as REM time, and also demonstrated subjective improvement in sleep quality [58]. Of course, medications with longer half-lives will have greater benefit during sleep as patients will not have to awaken to re-dose in the middle of the night. Treatment

with tiotropium improved spirometry, oxygen saturation in REM sleep, and TST with no adverse effects on sleep quality [59]. Studies of inhaled steroids used in combination suggest some treatment benefits for sleep. When fluticasone propionate with salmeterol was compared with ipratropium bromide/albuterol for the treatment of COPD, the fluticasone-salmeterol group experienced fewer nighttime awakenings, fewer sleep symptoms, and more albuterol-free nights [60]. Salmeterol alone was compared to placebo in 15 patients (12 completed the trial) in a randomized, placebo-controlled double-blind study for 4 weeks with salmeterol use resulting in improved mean oxygen saturation during sleep and less time at an oxygen saturation <90%, with no change in sleep quality [61]. Another randomized, placebo-controlled double-blind study of severe, stable COPD patients assessed the effects of tiotropium on SaO₂ and sleep quality [59]. This study also demonstrated higher SaO₂ during TST. Additionally the study reported more symptom-free nights, fewer nocturnal awakenings due to respiratory symptoms, improved sleep symptom scores, and reduced need for rescue medications. Newer long-acting β -agonists, anticholinergics, and anti-inflammatory agents hold promise in further reducing nocturnal symptoms in COPD patients [62].

Sleep Quality in COPD

Like patients with any chronic disease, patients with COPD who have perceptions of poor health are likely to experience anxiety, depression, sleep disturbance, and problems with daily functioning. Research shows that approximately 40–50% of COPD patients report depression and/or anxiety [63–65]. Insomnia is one of the diagnostic criteria for major depressive disorder. Additionally, insomnia may persist even during remission and be a marker for recurrence. Further, patients who experience major depressive disorder may be more likely to be nonresponders to antidepressant therapy and experience an increased risk of suicidal behavior. Clearly, depression in COPD patients has serious health consequences, and has been linked to higher mortality in these patients [66]. Yet consensus on how to manage insomnia in COPD is lacking.

Research has demonstrated that combining eszopiclone and fluoxetine may benefit patients with major depressive disorder and insomnia. In a randomized study [67], 545 patients who received fluoxetine in the morning were randomized to eszopiclone plus fluoxetine or pla-

cebo at night for 8 weeks. Patients who received combination therapy experienced significantly decreased sleep latency and wake time after sleep onset. Other benefits reported include increased TST, sleep quality, and depth of sleep at all double-blind time points (all $p < 0.05$). Eszopiclone co-therapy also resulted in significantly greater changes in the Hamilton Rating Scale for Depression (HAMD-17), which improved progressively ($p = 0.01$ week 4, and $p = 0.002$ week 8), and significantly improved Clinical Global Impressions scale scores ($p < 0.05$). There were also significantly more responders (59 vs. 48%; $p = 0.009$) and remitters (42 vs. 33%; $p = 0.03$) in patients receiving combination therapy. Discontinuation rates due to adverse effects were similar between the two treatment groups.

Despite these reported benefits, many clinicians hesitate to treat insomnia in the setting of COPD out of concern that hypnotics and other medications may further impair breathing. Whereas some sedatives and narcotics such as benzodiazepines and opioids worsen oxygen desaturation during sleep and are not recommended, some newer, non-benzodiazepine hypnotics appear to be safe in patients with mild-to-moderate COPD. Zolpidem and zopiclone have both been shown to improve sleep in COPD patients, and neither drug caused significant impairment in respiratory parameters [68–70]. Similarly, a recent study showed that a melatonin agonist, ramelteon, is also safe to use in COPD patients [71]. Although some patients use alcohol as a hypnotic, patients should be advised to refrain from alcohol use, particularly in the evenings, as heavy use has been associated with increased hypoventilation and ventricular ectopy [72, 73].

Management of comorbid depression and/or insomnia complaints in COPD patients requires careful consideration of the effects of medications. In addition to medications, alternative nonpharmacologic treatments should also be considered, such as cognitive behavioral therapy. Clearly, this is an area that deserves further study.

Conclusions

Sleep can have profound effects on ventilation in patients with COPD, and NOD is common in this setting. Prediction of the patients who are at risk for NOD is difficult. Although treatment of NOD has not been shown to increase overall survival rates, lack of treatment has been associated with a variety of medical problems, including sustained pulmonary hypertension and in-

creased mortality. Although in the setting of COPD clinicians are likely to ask patients about daytime drowsiness, they are unlikely to ask about insomnia and other sleep disturbances. Clinicians should consider treatment of comorbid sleep disturbances, including obstructive sleep apnea and insomnia, which may benefit the underlying COPD as well [15].

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