CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will consider the possibility that patients with either asthma or chronic obstructive pulmonary disease may also have obstructive sleep apnea, and vice versa

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The intersection of obstructive lung disease and sleep apnea

ABSTRACT

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) have synergistic detrimental effects. Their comorbid association leads to compromised gas exchange (hypoxia and hypercapnia) and higher rates of morbidity and death. As our understanding of the pathophysiologic processes of sleep evolves, the relationship between OSA and obstructive lung diseases such as COPD ("overlap syndrome") or asthma ("alternative overlap syndrome") has become more apparent. The pathophysiology of the combined conditions and optimal management are still being defined, but the effect on quality of life and morbidity underscore the importance of proper diagnosis and appropriately tailored management in these patients.

KEY POINTS

Obstructive lung diseases and OSA are both common and may exacerbate each other.

When assessing a patient with COPD, it may be prudent to think about whether the patient also has OSA, and vice versa.

Oxygen therapy lowers the risk of death in patients with COPD but may worsen hypercapnia and apneic episodes in those with OSA.

Continuous positive airway pressure is the first line of therapy for overlap syndrome. Daytime hypercapnia and nocturnal hypoxemia despite supplemental oxygen therapy are indications for nocturnal bilevel positive airway pressure therapy, regardless of the presence of OSA.

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Many patients who have obstructive lung disease, ie, chronic obstructive pulmonary disease (COPD) or asthma, also have obstructive sleep apnea (OSA), and vice versa.

The combination of COPD and OSA was first described almost 30 years ago by Flenley, who called it "overlap syndrome."[1] At that time, he recommended that a sleep study be considered in all obese patients with COPD who snore and in those who have frequent headaches after starting oxygen therapy. In the latter group, he doubted that nocturnal oxygen was the correct treatment. He also believed that the outcomes in patients with overlap syndrome were worse than those in patients with COPD or OSA alone. These opinions remain largely valid today.

We now also recognize the combination of asthma and OSA (alternative overlap syndrome) and collectively call both combinations obstructive lung disease-obstructive sleep apnea (OLDOSA) syndrome.[2] Interestingly, these relationships are likely bidirectional, with one condition aggravating or predisposing to the other.

Knowing that a patient has one of these overlap syndromes, one can initiate continuous positive airway pressure (CPAP) therapy, which can improve clinical outcomes.[3–6] Therefore, when evaluating a patient with asthma or COPD, one should consider OSA using a validated questionnaire and, if the findings suggest the diagnosis, polysomnography. Conversely, it is prudent to look for comorbid obstructive lung disease in patients with OSA, as interactions between upper and lower airway dysfunction may lead to distinctly different treatment and outcomes.

Here, we briefly review asthma and COPD, explore shared risk factors for sleep-disordered

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TABLE 1

Main differentiating and overlapping features of asthma and COPD

Feature	Asthma	COPD	Exceptions and overlapping features
Risk factors	Allergens	Smoking	Smoking may be an aggravating factor in asthma; children with early-life wheezing have a higher risk of developing asthma as teenagers and chronic obstructive pulmonary disease (COPD) as adults (the "Dutch hypothesis"); repeated airway infections may trigger development of either asthma or COPD, depending on the nature of infection and the intrinsic genetic predisposition (the "British hypothesis")
Anatomic segment involved	Airways	Airways and parenchyma	Severe asthma exacerbations may lead to adjacent parenchymal destruction, severe hyperinflation, and loss of scaffolding, or to radial or axial traction, or both, on the small airways
Atopy	Yes	No	Atopy may be present in some patients with COPD
Airway inflammation	Yes	Yes	Absent in mild asthma between exacerbations
Peripheral eosinophilia	Yes	No	Some patients with COPD may have eosinophilia; some patients with asthma may have neutrophilic infiltration (eg, severe asthma, asthma coexistent with gastroesophageal reflux and chronic rhinitis)
Airway eosinophilia	Yes	No	20%–40% of patients with COPD have airway eosinophilia (if one excludes eosinophilic bronchitis, up to 20% patients with COPD can still have some eosinophilic airway infiltration)
Exhaled gas (lower-airway) nitric oxide concentration	High	Low	May be reduced in some asthma phenotypes, eg, neutrophilic or paucigranulocytic; may be present in some patients with COPD
Diffusing lung capacity for carbon monoxide	Normal	Reduced (in emphysema)	Normal in chronic bronchitis; increased in acute asthma
Airway resistance	High	High	Normal in mild asthma between exacerbations; normal or slightly increased in emphysema
Airway hyperresponsiveness	Yes	No	May be present in COPD
Elastic recoil of the airways and parenchyma	Normal	Reduced (in emphysema)	Reduced in acute exacerbations of severe asthma; normal in chronic bronchitis
Symptoms	Episodic	Persistent	May be episodic in some patients with COPD, especially during significant environmental exposures
Comorbidities	Atopic dermatitis, allergic rhinitis	Cardiovascular disease	Obstructive sleep apnea may complicate both conditions

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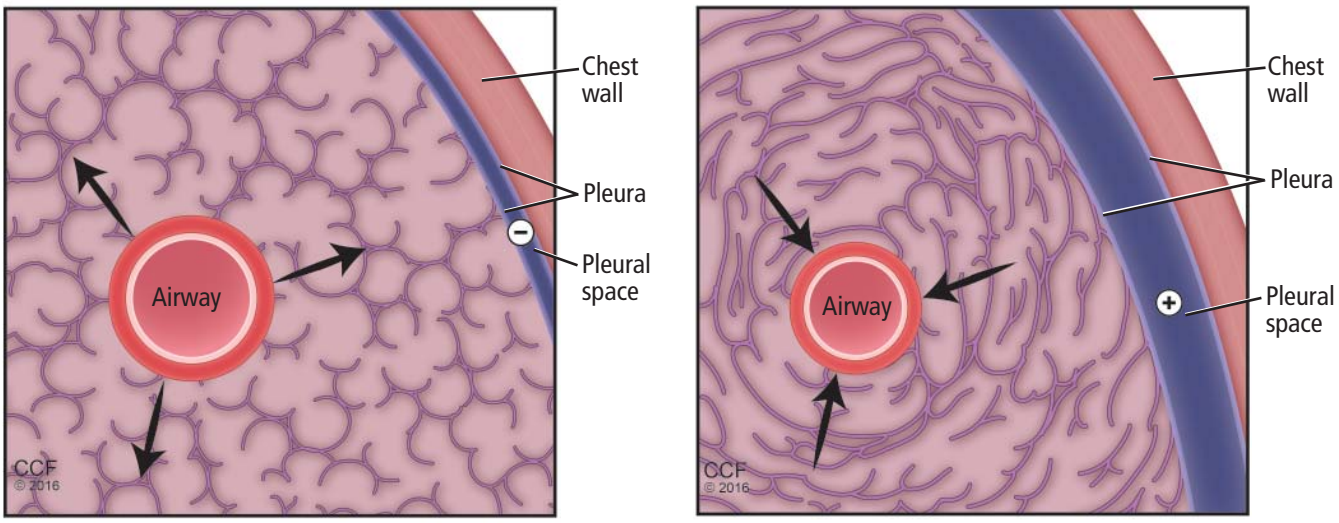
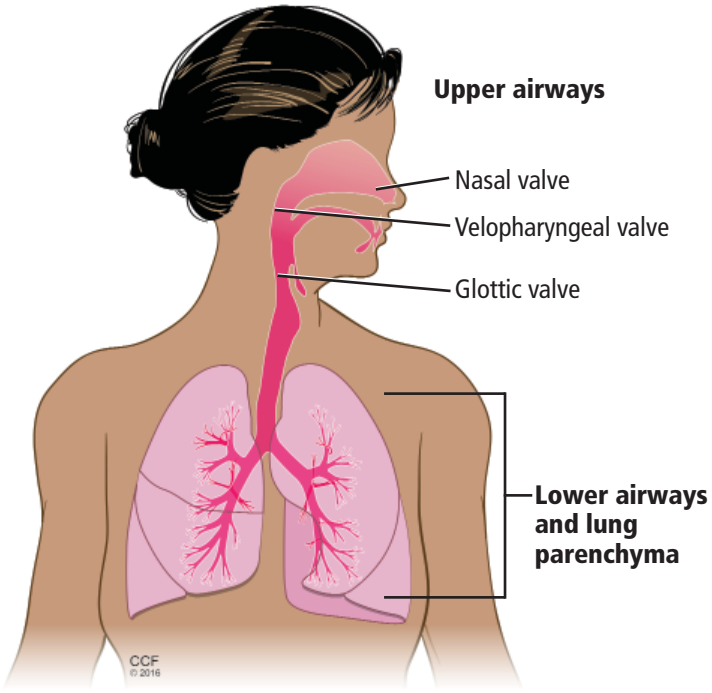


Radial coupling between airways and lung parenchyma during inspiration (left) and expiration (right) is affected by differences in upper airway resistance from obstructive sleep apnea;
(–) signifies subatmospheric pressure or pressure lower than mouth-level barometric pressure during inspiration;
(+) signifies supra-atmospheric pressure or pressure higher than mouth-level barometric pressure during expiration.



Axial coupling between upper airways, lower airways, and lung parenchyma (the basis of the "tracheal tug" theory).

FIGURE 1.

breathing and obstructive lung diseases, describe potential pathophysiologic mechanisms explaining these associations, and highlight the importance of recognizing and individually treating the overlaps of OSA and COPD or asthma.

COPD AND ASTHMA ARE VERY COMMON

About 10% of the US population have COPD,[7] a preventable and treatable disease mainly caused by smoking, and a leading cause of sickness and death worldwide.[8,9]

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About 8% of Americans have asthma,[7] which has become one of the most common chronic conditions in the Western world, affecting about 1 in 7 children and about 1 in 12 adults. The World Health Organization estimates that 235 million people suffer from asthma worldwide, and by 2025 this number is projected to rise to 400 million.[10,11]

The prevalence of these conditions in a particular population depends on the frequency of risk factors and associated morbidities, including OSA. These factors may allow asthma or COPD to arise earlier or have more severe manifestations.[8,12]

Asthma and COPD: similarities and differences

Asthma and COPD share several features. Both are inflammatory airway conditions triggered or perpetuated by allergens, viral infection, tobacco smoke, products of biomass or fossil fuel combustion, and other substances. In both diseases, airflow is "obstructed" or limited, with a low ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC). Symptoms can also be similar, with dyspnea, cough, wheezing, and chest tightness being the most frequent complaints. The similarities support the theory proposed by Orie et al[13] (the "Dutch hypothesis") that asthma and COPD may actually be manifestations of the same disease.

About 10% of the US population have COPD, and 8% have asthma

But there are also differences. COPD is strongly linked to cigarette smoking and has at least three phenotypes:

- Chronic bronchitis, defined clinically by cough and sputum production for more than 3 months per year for 2 consecutive years
- Emphysema, characterized anatomically by loss of lung parenchyma, as seen on tomographic imaging or examination of pathologic specimens
- A mixed form with bronchitic and emphysematous features, which is likely the most common.

Particularly in emphysematous COPD, smoking predisposes patients to gas-exchange abnormalities and low diffusing capacity for carbon monoxide.

In asthma, symptoms may be more episodic, the age of onset is often younger, and atopy is common, especially in allergic asthma. These episodic symptoms may correlate temporally with measurable airflow reversibility (≥ 12% and ≥ 200 mL improvement in FVC or in FEV_1 after bronchodilator challenge).

However, the current taxonomy does not unequivocally divide obstructive lung diseases into asthma and COPD, and major features such as airway hyperresponsiveness, airflow reversibility, neutrophilic or CD8 lymphocytic airway inflammation, and lower concentration of nitric oxide in the exhaled air may be present in different phenotypes of both conditions (**Table 1**).

AIRFLOW IN OBSTRUCTIVE LUNG DISEASES AND DURING SLEEP

Normal airflow involves a complex interplay between airway resistance and elastic recoil of the entire respiratory system, including the airways, the lung parenchyma, and the chest wall (**Figure 1**).

In asthma and COPD, resistance to airflow is increased, predominantly in the upper airways (nasal passages, pharynx, and larynx) and in the first three or four subdivisions of the tracheobronchial tree. The problem is worse during exhalation, when elastic recoil of the lung parenchyma and chest wall also increases airway resistance, reduces airway caliber, and possibly even constricts the bronchi. This last effect may occur either due to mass loading of the bronchial smooth muscles or to large intrathoracic transmural pressure shifts that may increase extravasation of fluid in the bronchial walls, especially with higher vascular permeability in inflammatory conditions.

Furthermore, interactions between the airway and parenchyma and between the upper and lower airways, as well as radial and axial coupling of these anatomic and functional components, contribute to complex interplay between airway resistance and parenchymal-chest wall elastic energy—stretch or recoil.

The muscles of the upper and lower airway may not work together due to the loss of normal lung parenchyma (as in emphysema) or to the acute inflammation in the small airways and adjacent parenchyma (as in severe asthma exacerbations). This loss of coordination makes the upper airway more collapsible,

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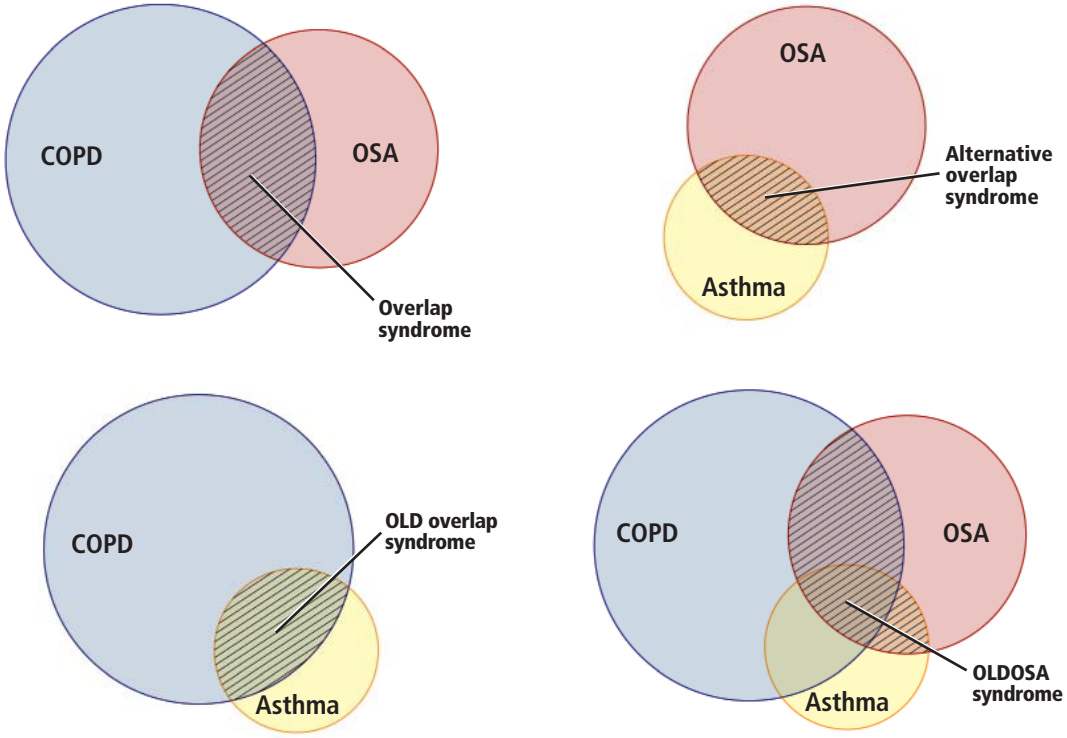

FIGURE 2. The main overlap syndromes. Sizes of circles roughly correspond to prevalences of the diseases they represent. COPD = chronic obstructive pulmonary disease; OLD = obstructive lung disease; OLDOSA = obstructive lung disease and obstructive sleep apnea; OSA = obstructive sleep apnea. OLD overlap syndrome has also been called asthma-COPD overlap syndrome.

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a feature of OSA.

Additionally, obesity, gastroesophageal reflux, disease chronic rhinitis, nasal polyposis, and acute exacerbations of chronic systemic inflammation all contribute to more complex interactions between obstructive lung diseases and OSA.[6]

Sleep affects breathing, particularly in patients with respiratory comorbidities, and sleep-disordered breathing causes daytime symptoms and worsens quality of life.[1,13–15] During sleep, respiratory centers become less sensitive to oxygen and carbon dioxide; breathing becomes more irregular, especially during rapid eye movement (REM) sleep; the chest wall moves less, so that the tidal volume and functional residual capacity are lower; sighs, yawns, and deep breaths become limited; and serum carbon dioxide concentration may rise.

OBSTRUCTIVE SLEEP APNEA

The prevalence of OSA, a form of sleep-disordered breathing characterized by limitation of inspiratory and (to a lesser degree) expiratory flow, has increased significantly in recent years, in parallel with the prevalence of its major risk factor, obesity.

OSA is generally defined as an apnea-hypopnea index of 5 or higher, ie, five or more episodes of apnea or hypopnea per hour.

OSA syndrome, ie, an apnea-hypopnea index of 5 or higher and excessive daytime sleepiness (defined by an Epworth Sleepiness Scale score > 10) was found in the initial analysis of the Wisconsin Sleep cohort in 1993 to be present in about 2% of women and 4% of men.[16] A more recent longitudinal analysis showed a significant increase—for example, in people 50 to 70 years old the prevalence was

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up to 17.6% in men and 7.5% in women.[17]

Upper airway resistance syndrome, a milder form of sleep-disordered breathing, is now included under the diagnosis of OSA, as its pathophysiology is not significantly different.[18]

In the next section, we discuss what happens when OSA overlaps with COPD (overlap syndrome) and with asthma ("alternative overlap syndrome")[2,8] (**Figure 2**).

OSA AND COPD (OVERLAP SYNDROME)

Flenley[1] hypothesized that patients with COPD in whom supplemental oxygen worsened hypercapnia may also have OSA and called this association overlap syndrome.

How common is overlap syndrome?

Since both COPD and OSA are prevalent conditions, overlap syndrome may also be common.

The reported prevalence of overlap syndrome varies widely, depending on the population studied and the methods used. In various studies, COPD was present in 9% to 56% of patients with OSA,[19–23] and OSA was found in 5% to 85% of patients with COPD.[24–27]

The 'Dutch hypothesis': asthma and COPD are manifestations of the same disease

Based on the prevalence of COPD in the general population (about 10%[12]) and that of sleep-disordered breathing (about 5% to 10%[17]), the expected prevalence of overlap syndrome in people over age 40 may be 0.5% to 1%.[28] In a more inclusive estimate with "subclinical" forms of overlap syndrome—ie, OSA defined as an apnea-hypopnea index of 5 or more (about 25% of the population[17]) and COPD Global initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (16.8% in the National Health and Nutrition Education Survey[12])—the expected prevalence of overlap is around 4%. Some studies found a higher prevalence of COPD in OSA patients than in the general population,[21,29] while others did not.[22,28,30] The studies differed in how they defined sleep-disordered breathing.

Larger studies are needed to better assess the true prevalence of sleep-disordered breathing in COPD. They should use more sensitive measures of airflow and standardized definitions of sleep-disordered breathing and should include patients with more severe COPD.

Fatigue and insomnia are common in COPD

Fatigue is strongly correlated with declining lung function, low exercise tolerance, and impaired quality of life in COPD.[31] Factors that contribute to fatigue include dyspnea, depression, and impaired sleep.[32] Some suggest that at least half of COPD patients have sleep complaints such as insomnia, sleep disruption, or sleep fragmentation.[33] Insomnia, difficulty falling asleep, and early morning awakenings are the most common complaints (30%–70% of patients) and are associated with daytime fatigue.[34] Conversely, comorbid OSA can contribute to fatigue and maintenance-type insomnia (ie, difficulty staying asleep and returning to sleep).

Multiple mechanisms of hypoxemia in overlap syndrome

Oxygenation abnormalities and increased work of breathing contribute to the pathophysiology of overlap syndrome. In patients with COPD, oxygenation during wakefulness is a strong predictor of gas exchange during sleep.[35] Further, patients with overlap syndrome tend to have more severe hypoxia during sleep than patients with isolated COPD or OSA at rest or during exercise.[36]

In overlap syndrome, hypoxemia is the result of several mechanisms:

- Loss of upper airway muscle tone from intermittent episodes of obstructive apnea and hypopnea leads to upper airway collapse during sleep, particularly during REM sleep, increasing the severity of OSA.[37]
- Reductions in functional residual capacity from lying in the recumbent position and during REM sleep render patients with COPD more vulnerable, as compensatory use of accessory muscles to maintain near-normal ventilation in a hyperinflated state becomes impaired.[37]
- Alterations in pulmonary ventilation-perfusion matching may lead to altered carbon dioxide homeostasis and impaired oxygenation in patients with emphysema.
- Circadian variation in lower airway caliber may also be observed, in parallel with the bronchoconstriction caused by increased nocturnal vagotonia.
- Hypercapnia ($Paco_2 \geq 45$ mm Hg) may lead to overall reduced responsiveness of re-

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spiratory muscles and to a blunted response of respiratory centers to low oxygen and high carbon dioxide levels.[38] Thus, hypercapnia is a better predictor of the severity of nocturnal hypoxemia than hypoxemia developing during exercise.[39]

In a person who is at near-maximal ventilatory capacity, even a mild increase in upper airway resistance (as seen with snoring, upper airway resistance syndrome, or OSA) increases the work of breathing. This phenomenon can lead to early arousals even before significant oxyhemoglobin desaturation occurs.

Normally, inspiratory flow limitation is counteracted by increasing inspiratory time to maintain ventilation. Patients with COPD may not be able to do this, however, as they need more time to breathe out due to narrowing of their lower airways.[40] The inability to compensate for upper airway resistance, similar to the increased work of breathing seen with exercise, may lead to early arousals and increased sleep fragmentation.

Consequences of overlap syndrome

Patients with overlap syndrome appear to have higher morbidity and mortality rates than those with COPD or sleep-disordered breathing alone.

Cor pulmonale. Nighttime hypoxia is more severe and persistent in overlap syndrome than with COPD or OSA alone. This may contribute to more significant pulmonary hypertension and to the development of cor pulmonale, in which the right ventricle is altered in structure (eg, hypertrophied, dilated) or reduced in function, or both, from severe pulmonary hypertension.

In contrast to right ventricular failure due to disorders of the left heart, cor pulmonale is a result of diseases of the vasculature (eg, idiopathic pulmonary arterial hypertension), lung parenchyma (eg, COPD), upper airway (eg, OSA), or chest wall (eg, severe kyphoscoliosis). COPD is the most common cause of cor pulmonale in the United States, accounting for up to 30% of cases of cor pulmonale.[41–45] In OSA, cor pulmonale is seen in up to 20% of cases,[43] while in overlap syndrome cor pulmonale is encountered even more often (ie, in up to 80%); these patients have a dismal 5-year survival rate of about 30%.[46]

Obesity hypoventilation syndrome is characterized by obesity (body mass index ≥ 30 kg/m^2) and daytime hypercapnia ($Paco_2$ ≥ 45 mm Hg) that cannot be fully attributed to an underlying cardiopulmonary or neurologic condition.[18] Hypercapnia worsens during sleep (especially during REM sleep) and is often associated with severe arterial oxygen desaturation. Up to 90% of patients with obesity hypoventilation syndrome have comorbid OSA, and the rest generally have sleep-related hypoventilation, particularly during REM sleep.

In patients with obesity hypoventilation syndrome, daytime hypercapnia may improve or even normalize with adequate positive airway pressure treatment and sustained adherence to treatment.[18] Many patients with obesity hypoventilation syndrome respond to CPAP or bilevel positive airway pressure (BPAP), with improvement in daytime $Paco_2$. However, normalization of daytime $Paco_2$ occurs only in a subgroup of patients. In contrast, treatment with oxygen therapy alone may worsen hypercapnia.

Oxygen therapy for pure COPD, but maybe not for overlap syndrome

Continuous oxygen therapy reduces mortality in COPD,[47,48] but the duration and severity of hypoxemia that warrant oxygen therapy are less clear. Oxygen therapy in hypoxemic patients has been shown to improve sleep quality and reduce arousals.[49]

Indications for oxygen treatment of nocturnal hypoxemia are generally based on Medicare guidelines:

- At least 5 minutes of sleep with peripheral oxygen saturation ≤ 88% or Pao_2 ≤ 55 mm Hg, or
- A decrease in Pao_2 of more than 10 mm Hg or in peripheral oxygen saturation of more than 5% for at least 5 minutes of sleep and associated with signs or symptoms reasonably attributable to hypoxemia (group I criteria), or
- At least 5 minutes of sleep with peripheral oxygen saturation ≥ 89% or Pao_2 56 to 59 mm Hg and pedal edema, pulmonary hypertension, cor pulmonale, or erythrocytosis (group II criteria).[50]

The prevalence of obstructive sleep apnea has increased in parallel with that of obesity

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Approximately 47% of COPD patients who are hypoxemic during the day spend about 30% of sleep time with an oxygen saturation less than 90%, even while on continuous oxygen therapy.[51] Current recommendations for nocturnal oxygen therapy are to increase the oxygen concentration by 1 L/minute above the baseline oxygen flow rate needed to maintain an oxygen saturation higher than 90% during resting wakefulness, using a nasal cannula or face mask.[52]

Caveat. *In overlap syndrome, supplemental oxygen may prolong the duration of apnea episodes and worsen hypercapnia.*

Positive airway pressure for OSA

Positive airway pressure therapy improves cardiovascular outcomes in OSA.[53] Several studies[54–58] compared the effectiveness of CPAP vs BPAP as initial therapy for OSA but did not provide enough evidence to favor one over the other in this setting. Similarly, the results are mixed for the use of fixed or auto-adjusting BPAP as salvage therapy in patients who cannot tolerate CPAP.[59–61]

In overlap syndrome, CPAP or BPAP with or without supplemental oxygen has been investigated in several studies.[26,62–65] In general, the mortality rate of COPD patients who require oxygen therapy is quite high.[47,66] In hypoxemic COPD patients with moderate to severe sleep-disordered breathing, the 5-year survival rate was 71% in those treated with CPAP plus oxygen, vs 26% in those on oxygen alone, independent of baseline postbronchodilator FEV_1.[67]

At near-maximal ventilatory capacity, even a mild increase in upper airway resistance increases the work of breathing

There is no specific FEV_1 cutoff for prescribing CPAP. In general, daytime hypercapnia and nocturnal hypoxemia despite supplemental oxygen therapy are indications for BPAP therapy, regardless of the presence of OSA. Whether noninvasive nocturnal ventilation for COPD patients who do not have OSA improves long-term COPD outcomes is not entirely clear.[65,68,69]

Adding nocturnal BPAP in spontaneous timed mode to pulmonary rehabilitation for severe hypercapnic COPD was found to improve quality of life, mood, dyspnea, gas exchange, and decline in lung function.[70] Other studies noted that COPD patients hospitalized with respiratory failure who were randomized to noninvasive nocturnal ventilation plus oxygen therapy as opposed to oxygen alone experienced improvement in health-related quality of life and reduction in intensive-care-unit length of stay but no difference in mortality or subsequent hospitalizations.[69] In stable hypercapnic COPD patients without OSA, there is no clear evidence that nocturnal noninvasive ventilation lessens the risk of death despite improved daytime gas exchange,[71,72] but additional long-term studies are needed.

Lung volume reduction surgery, a procedure indicated for highly selected patients with severe COPD, has been shown to reduce hyperinflation, improve nocturnal hypoxemia, and improve total sleep time and sleep efficiency in patients without sleep-disordered breathing.[73] More studies are needed to determine if reduction in lung hyperinflation has an impact on the occurrence of OSA and on morbidity related to sleep-disordered breathing.

Benefit of CPAP in overlap syndrome

In a nonrandomized study, Marin et al[62] found that overlap syndrome is associated with an increased risk of death and hospitalization due to COPD exacerbations. CPAP therapy was associated with improved survival rates and decreased hospitalization rates in these patients.

Stanchina et al,[74] in a post hoc analysis of an observational cohort, assessed the outcomes of 227 patients with overlap syndrome. Greater use of CPAP was found to be associated with lower mortality rates.

Jaoude et al[75] found that hypercapnic patients with overlap syndrome who were adherent to CPAP therapy had a lower mortality rate than nonadherent hypercapnic patients ($P = .04$). In a multivariate analysis, the comorbidity index was the only independent predictor of mortality in normocapnic patients with overlap syndrome, while CPAP adherence was associated with improved survival.

Lastly, patients with overlap syndrome tend to need more healthcare and accrue higher medical costs than patients with COPD alone. An analysis of a state Medicaid database that included COPD patients showed that beneficiaries with overlap syndrome spent at least

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$4,000 more in medical expenditures than beneficiaries with "lone" COPD.[24]

In conclusion, CPAP is the first line of therapy for overlap syndrome, while daytime hypercapnia or nocturnal hypoxemia despite supplemental oxygen therapy are indications for nocturnal BPAP therapy, regardless of whether patients have OSA.

OSA AND ASTHMA (ALTERNATIVE OVERLAP SYNDROME)

Epidemiology and clinical features

The coexistence of asthma and OSA can begin in childhood and continue throughout adult life. A higher prevalence of lifetime asthma and OSA has been noted in children of racial and ethnic minorities, children of lower socioeconomic status, and those with atopy.[76]

In a pediatric asthma clinic, it was noted that 12 months into structured asthma management and optimization, children with sleep-disordered breathing were nearly four times more likely to have severe asthma at follow-up, even after adjusting for obesity, race, and gender.[77]

In adult patients with OSA, the prevalence of asthma is about 35%.[78] Conversely, people with asthma are at higher risk of OSA. High risk of OSA was more prevalent in a group of patients with asthma than in a general medical clinic population (39.5% vs 27.2%, $P < .05$).[79]

Analysis of a large prospective cohort found that asthma was a risk factor for new-onset OSA. The incidence of OSA over 4 years in patients with self-reported asthma was 27%, compared with 16% without asthma. The relative risk adjusted for risk factors such as body mass index, age, and gender was 1.39 (95% confidence interval [CI] 15%–19%).[80]

Patients with asthma who are at high risk of OSA are more likely to have worse daytime and nighttime asthma symptoms. Interestingly, patients who are diagnosed with OSA and treated with CPAP seem to have better asthma control.

Patients with asthma who are more likely to have OSA are women (odds ratio [OR] 2.1), have greater asthma severity (OR 1.6), have gastroesophageal reflux disease (OR 2.7), and use inhaled corticosteroids (OR 4.0).[81] These associations are different than the traditional, population-wide risk factors for OSA, such as male sex, excess body weight, and nocturnal nasal congestion.[82]

OSA also worsens asthma control. Teodorescu et al[15] found that severe asthma was more frequent in older asthma patients (ages 60–75, prevalence 49%) than in younger patients (ages 18–59, 39%). Older adults with OSA were seven times as likely to have severe asthma (OR 6.6), whereas young adults with sleep apnea were only three times as likely (OR 2.6).

In a group of patients with difficult-to-treat asthma, OSA was significantly associated with frequent exacerbations (OR 3.4), an association similar in magnitude to that of psychological conditions (OR 10.8), severe sinus disease (OR 3.7), recurrent respiratory tract infections (OR 6.9), and gastroesophageal reflux disease (OR 4.9).[83] More than half of the patients had at least three of these comorbid conditions.

Sleep quality can greatly affect asthma control, and its importance is often underestimated. Patients with severe asthma have worse sleep quality than patients with milder asthma or nonasthmatic patients, even after excluding patients with a high risk of OSA, patients on CPAP therapy, and patients with a history of gastroesophageal reflux disease. Furthermore, regardless of asthma severity, sleep quality is a significant predictor of asthma-related quality of life, even after accounting for body mass index, daytime sleepiness, and gastroesophageal reflux disease.[84]

Overlap syndrome with cor pulmonale typically has a poor prognosis; one study found a 5-year survival rate of 30%

Pathophysiology of alternative overlap syndrome

Sleep significantly affects respiratory pathophysiology in asthma. The underlying mechanisms include physical and mechanical stressors, neurohormonal changes, hypoxia, confounding medical conditions, and local and systemic inflammatory changes.

Patients with nocturnal asthma experience more pronounced obstruction when sleep-deprived, suggesting that sleep loss may contribute to worsening airflow limitation.[14] Although changes in pulmonary mechanics and lung volumes may also have a role, volume-dependent airway narrowing does not appear to account for all observed nocturnal increases in airway resistance. Intrathoracic

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TABLE 2

Proposed ABCD-3P-PQRST characterization system for asthma phenotypes, genotypes, and endotypes

ABCD	3P model[a]	PQRST	
Asthmatic symptoms	**P**aroxysmal (< 1 month) **P**ersistent (1–6 months) **P**ermanent (> 6 months)	**P**recipitating factors	Exertion (during, after), allergens, odors, drugs, tobacco smoke
		Qualitative description	Cough, wheezing, chest tightness, dyspnea
		Reversibility to bronchodilator	Absolute change, percent change
		Severity	Mild intermittent, mild, moderate, severe, or very severe persistent
		Type	Onset (adulthood or childhood), race and ethnicity, gender (male or female, prepubertal, adult, postmenopausal)
Biomarkers	**P**redominant cells	Effector cells: eosinophils, neutrophils, mast cells, mixed cellularity, paucicellular Lymphocytes: T-helper 1 (Th1), Th2, Th17, regulatory T lymphocyes, natural killer cells	
	Predominant cytokines, immunoglobulins, molecules	Interleukin (IL) 4, IL-5, IL-9, IL-13, IL-33, periostin; interferon gamma, IL-15, IL-17, IL-18, IL-21, IL-22; immunoglobulin E or G; nitric oxide	
	Predisposing genotype	Specific gene polymorphisms, mutations	
Conditions associated	**P**renatal risk factors	Maternal smoking, diet, nutrition, antibiotic use, stress	
	Postnatal risk factors	Early-life wheezing, breastfeeding, early tobacco smoke exposure, viral infections, vitamin D deficiency, contact with animals, occupational exposures	
	Pathogenically linked conditions	Atopy, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, obstructive sleep apnea, gastroesophageal reflux disease, obesity, bronchiectases	
Drugs used	Anticholinergics (short-acting and long-acting), beta-2 adrenergic agonists (short-acting and long-acting), corticosteroids (inhaled, oral), leukotriene pathway-modifying agents (eg, leukotriene receptor agonists, lipooxygenase inhibitors), phosphodiesterase inhibitors (eg, theophylline, roflumilast), cromolyn, nedocromil, mast cell stabilizers, anti–IL-5 agents (eg, mepolizumab, benralizumab, reslizumab), anti–IL-13 agents (eg, lebrikizumab, tralokinumab), anti-IgE (eg, omalizumab), anti-tumor necrosis factor alpha (golimumab)		

[a] 3P model for disease persistence should be characterized clinically, functionally, and biologically (eg, including exhaled gas concentration of nitric oxide).

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blood pooling may also contribute to nocturnal bronchoconstriction through stimulation of pulmonary C fibers and increased bronchial wall edema, a mechanism that may be similar to the "cardiac asthma" seen in left ventricular dysfunction.

Early studies of sleep-disordered breathing demonstrated that patients with asthma were breathing more irregularly (with hypopnea, apnea, and hyperpnea) in REM sleep than those without asthma.[85] Interestingly, REM-related hypoxia has also been noted in children with asthma.[86] This may be related to the increased cholinergic outflow that occurs during REM sleep, which in turn modulates the caliber and reactivity of the lower airways.

Physical changes such as upper airway collapse and reduced pharyngeal cross-sectional area may cause further mechanical strain.[87] This can further propagate airway inflammation, alter airway mucosal muscle fibers, and stimulate neural reflexes, thereby increasing cholinergic tone and bronchoconstriction. Furthermore, heightened negative intrathoracic pressure during obstructive episodes can increase nocturnal pulmonary blood pooling.[14] Hypoxia itself can augment airway hyperresponsiveness via vagal pathways or carotid body receptors, increasing reactive oxygen species and inflammatory mediators. Local inflammation can "spill over" into systemic inflammatory changes, while alterations in airway inflammatory markers in asthma seem to follow a circadian rhythm, in parallel with the nocturnal worsening of the asthma symptoms.[88] Finally, altered sleep may be related to other comorbid conditions, such as gastroesophageal reflux disease, insomnia, and restless leg syndrome.

Management and outcomes of alternative overlap syndrome

Despite optimization of asthma management, OSA can still significantly affect asthma control and symptoms.[84]

Interestingly, medications that reduce airway inflammation (eg, corticosteroids) may promote OSA. This occurrence cannot be fully explained by an increase in body mass, as more respiratory disturbances occur during sleep with continuous corticosteroid treatment even without increases in body mass index.[87] Therefore, these associations may be related to upper airway myopathy caused by the treatment, a small pharynx, facial dysmorphisms, or fat deposition.[89]

Does CPAP improve asthma?

OSA is often unrecognized in patients with asthma, and treating it can have an impact on asthma symptoms.

CPAP therapy has not been shown to significantly change airway responsiveness or lung function, but it has been noted to significantly improve both OSA-related and asthma-related quality of life and reduce the use of rescue bronchodilators.[3,90] CPAP has demonstrated improvement of quality of life that positively correlated with body weight and apnea-hypopnea index at baseline, suggesting that asthmatic patients with greater obesity or worse OSA may benefit most from aggressive management.[90]

However, CPAP should be used only if the patient has confirmed OSA. Empiric use of CPAP without a diagnosis of OSA was poorly tolerated and failed to improve asthma symptoms or lung function.[91] More importantly, using CPAP in a patient who does not have OSA may contribute to further sleep disruption.[91]

Second-line treatments such as mandibular advancing devices and airway or bariatric surgery have not yet been studied in alternative overlap syndrome.

In overlap syndrome, oxygen may prolong the duration of apnea episodes and worsen hypercapnia

A multidimensional assessment of asthma

The Western world is experiencing an epidemic of obesity and of asthma. Obesity contributes to the pathogenesis of OSA by altering the anatomy and collapsibility of the upper airway, affecting ventilatory control and increasing respiratory workload. Another paradigm, supported by some evidence, is that OSA itself may contribute to the development of obesity. Both OSA and obesity lead to activation of inflammatory biologic cascades, which are likely the pathogenic mechanisms for their cardiovascular and metabolic consequences. As such, early recognition of OSA is important, as effective treatments are available.

In some patients, obesity may cause asthma, as obesity precedes the onset of asthma in a significant proportion of patients, and bariatric surgery for morbid obesity may resolve

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asthma. The obese asthma phenotype seems to include chronic rhinosinusitis, gastroesophageal reflux disease, poorer asthma control, limited responsiveness to corticosteroids, and even different sets of biomarkers (eg, neutrophilic airway inflammation). A cohort of obese patients with poor asthma control demonstrated significant improvement in asthma symptoms, quality of life, and airway reactivity after weight loss from bariatric surgery.[92]

To improve our knowledge about airway disease phenotypes and endotypes and their response to therapy, we propose taking a multidimensional, structured assessment of all patients with asthma, using a schema we call "ABCD-3P-PQRST" (**Table 2**).

The purpose of using this type of system in clinics and research is to capture the multidimensionality of the disease and better develop future individualized therapeutic strategies by employing the latest advances in systems biology and computational methods such as cluster and principal component analysis.

Multidimensional assessments addressing airway problems such as asthma, COPD, OSA, other comorbidities and risk factors, and personalized management plans will need to be the basis of future therapeutic interventions. Increased attention to the complications of asthma and obstructive airway and lung diseases in our patients is imperative, specifically to develop effective systems of care, appropriate clinical guidelines, and research studies that lead to improved health outcomes. ■

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