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METHODS

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A review of therapies for the overlap syndrome of obstructive sleep apnea and chronic obstructive pulmonary disease

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Abstract

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are common chronic diseases. These two noncommunicable diseases (NCDs) are prevalent among approximately 10% of the general population. Approximately 1% of the population is affected by the co-existence of both conditions, known as the overlap syndrome (OS). OS patients suffer from greater degrees of nocturnal oxygen desaturation and cardiovascular consequences than those with either condition in isolation. Besides OS, patients with COPD may suffer from a spectrum of sleep-related breathing disorders, including hypoventilation and central sleep apnea. The article provides an overview of the pathogenesis, associated risk factors, prevalence, and management of sleep-related breathing disorders in COPD. It examines respiratory changes during sleep caused by COPD and OSA. It elaborates upon the factors that link the two conditions together to lead to OS. It also discusses the clinical evaluation and diagnosis of these patients. Subsequently, it reviews the pathophysiological basis and the current evidence for three potential therapies: positive airway pressure therapy [including continuous positive airway pressure (CPAP) and bilevel positive airway pressure], oxygen therapy, and pharmacological therapy. It also proposes a phenotypic approach toward the diagnosis and treatment of OS and the entire spectrum of sleep-related breathing disorders in COPD. It concludes with the current evidence gaps and future areas of research in the management of OS.

KEYWORDS

COPD, OSA, overlap syndrome, PAP therapy, phenotype, sleep-disordered breathing

1 | INTRODUCTION

Human beings spend one-third of their lifetimes in sleep, which is essential for restoration of physical and mental functions of the body.[1] However, an estimated 45% of the world's population experiences issues with sleep that affect their health and quality of life.[2] Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) and are common chronic diseases, both affected by and affecting sleep. These two noncommunicable diseases (NCDs) are prevalent among approximately 10% of the general population each and are gradually increasing in prevalence worldwide.[3,4] Approximately 1% of

the population is affected by the co-existence of both conditions, known as the overlap syndrome (OS).[3]

In this manuscript, we will review the respiratory changes during sleep in normal individuals as well as the pathophysiological changes during sleep in OSA and COPD. We will examine the factors that link the two conditions together to lead to OS. We will discuss the prevalence, costs, pathogenesis, risk factors, and clinical evaluation of OS and other sleep-related breathing disorders (SRBD) in COPD. Subsequently, we will review the pathophysiological basis and the current evidence for three potential therapies: positive airway pressure (PAP) therapy, oxygen therapy, and pharmacological therapy. We will also propose a phenotype-guided to approach to the management of these patients. Finally, we will identify evidence gaps and future areas of research in the management of OS.

2 | SLEEP AND BREATHING

Sleep and the respiratory system are intimately linked. A myriad of changes effect respiration during various phases of normal human sleep. These respiratory changes during sleep bear no adverse consequences for a healthy individual, however they can be detrimental for patients with disease states including obesity, chronic respiratory, and cardiac disease. The physiological changes during sleep affect the neural and chemical control of respiration, the respiratory muscles, and the upper airways.

First, there is diminished neural input to the brainstem respiratory centers from the higher centers during sleep which lessens the respiratory drive.[5] This is associated with a fall in the ventilation and consequential blood gas changes: a slight fall in the arterial partial pressure of oxygen (PaO_2) and a slight rise in the arterial partial pressure of carbon dioxide ($PaCO_2$).[6] This leads to an enhanced dependency on the chemoreceptors for chemical control of respiration in response to blood gas changes.[7] Secondly, the activity of the non-diaphragm respiratory muscles (i.e., the accessory muscles) is diminished during sleep and may be completely absent during rapid eye movement (REM) sleep.[8] Finally, the muscle tone of the pharyngeal dilator muscles which maintain the upper airway patency is reduced during sleep, especially during REM sleep.[9]

3 | OBSTRUCTIVE SLEEP APNEA (OSA)

OSA is the most common SRBD. OSA causes episodic collapse in the upper airway while sleeping resulting in momentary cessation or attenuation of breathing.[10] OSA affects an estimated 936 million adults aged 30–69 years old globally, of whom an estimated 425 million have moderate to severe disease.[11] Obesity is a major risk factor for OSA.[12] OSA is also a major risk factor for other NCDs, notably cardiovascular disease (CVD), metabolic disorders, hypertension, depression, and stroke.[10,12-16]

The economic burden of OSA is high.[15,17] In 2015, the estimated annual cost of OSA for USA was US $12.4 billion.[11] A study of the Danish National Patient Registry found that OSA resulted in annual health care costs 2.8 times higher than the average annual health cost for up to 12 years before OSA diagnosis, compared with control subjects of comparable age-, sex- and socioeconomic indicators.[17,18] OSA which is untreated or diagnosed late can double medical expenses due to comorbidity with CVD.[17] An estimated 80% of individuals with OSA are diagnosed late, even if they have access to health care.[16] In a US study, the upper third with most severe cases of OSA and comorbidities consumed 65–82% of all OSA patients' costs.[17]

3.1 | Respiratory changes during sleep in OSA

The number of obstructive events (apneas or hypopneas) occurring per hour of sleep is referred to as the apnea-hypopnea index (AHI), with a value greater than 5 events/hour usually denoting a diagnosis of OSA. The most important risk factor for OSA is obesity which leads to fat deposition in the neck structures with narrowing of the upper airway. Hence, when the pharyngeal dilator muscles become hypotonic during sleep, there is an increased tendency for the upper airway to collapse.[9] These episodic obstructive events lead to transient oxygen desaturations or "intermittent hypoxemia."[19]

Patients with more severe obesity have heavier loads imposed upon the respiratory muscles on account of the thicker chest wall. Simultaneously, the diaphragm is compressed by the abdominal fat leading to pulmonary restriction.[20] These factors may lead to profound hypoventilation during sleep, when there is reduced respiratory drive and respiratory muscle activity. Furthermore, obesity is associated with resistance to leptin. Resistance to this hormone has been implicated in reduced neural drive leading to central hypoventilation.[21] Hence, patients with severe obesity and SRBD may develop persistent hypercapnia termed as the obesity hypoventilation syndrome (OHS).

4 | CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD refers to respiratory disease due to noxious stimuli which is characterized by irreversible or incompletely

reversible airflow obstruction. The primary cause of COPD is first- or second-hand tobacco smoke. Additional environmental risk factors include exposure to indoor and outdoor pollution, dust, and hazardous fumes.[22] According to the Global Disease Burden Study of 2017, an estimated 272 million people worldwide are afflicted with COPD.[23] In 2017, COPD led to 3.2 million deaths worldwide.[23] Over 90% of deaths from COPD are in low- and middle-income countries.[22] In 2017, COPD was seventh leading cause of years of life lost. By 2040, it is expected to be the fourth leading cause.[23] Patients with COPD may suffer from a spectrum of SRBD, including OSA, sleep-related hypoventilation, and central sleep apnea (CSA).

4.1 | Respiratory changes during sleep in COPD

In patients with COPD, the respiratory changes during sleep underlie a spectrum of SRBD. COPD is not a homogenous disease entity and it may manifest with varying degrees of chronic bronchitis and emphysema.[4] Among patients with predominant emphysema, there is pre-existing downward displacement of the diaphragm which is worsened during sleep. This puts the diaphragm at a mechanical disadvantage for breathing which is compensated using the accessory muscles during the awake state. However, during sleep (especially REM stage) there is diminished function of the accessory muscles, which may worsen hypoventilation in these patients.[24] This results in frequent awakenings, reduced sleep efficiency and quality, and reduced REM sleep in COPD patients.[25] Thus, patients with COPD have sustained hypoxemia during sleep due to a combination of ventilation-perfusion mismatch and hypoventilation.[26]

5 | OVERLAP SYNDROME (OS)

OS refers to the co-existence of the OSA and COPD in the same patient.[27] The co-existence of the two conditions due to chance alone can yield a population prevalence of 1%.[4] Bednarek et al showed the prevalence of OS to be 1% in a population study and concluded that neither OSA predisposes for COPD, nor vice versa.[3] Other epidemiological studies have produced high variable results, possibly due to confounding risk factors in the studied samples. For instance, the prevalence of OSA in COPD patients has varied from 11% to 45%.[28-31] On the other hand, the prevalence of COPD in OSA patients has ranged from 9% to 41% in different studies.[3,31-33] It is also emphasized that definitions of OSA and COPD have varied between studies. Different apnea hypopnea index (AHI) cutoffs have been used to diagnose OSA in these studies.

Patients with COPD with predominant emphysema and severe airflow obstruction may be protected against developing OSA. This is because the hyperinflated emphysematous lungs reduce the collapsibility of the upper airways by a caudal traction effect.[34] Patients with severe COPD and emphysema also have lower body mass indices (BMIs), which is also protective against OSA.[35] In contrast, patients with relatively mild COPD who have a higher BMI tend to develop OSA, leading to the OS at a younger age.[28,34,36] These patients may be heavy smokers with higher cumulation of pack-years, which contributes to upper airway inflammation and OSA.[30,37] Furthermore, they often develop right heart failure at an earlier age. These patients experience rostral fluid shifts at night which worsens obstructive events due to edema of neck structures.[38]

Hence, the complex interaction between sleep, body-mass index, and COPD may either prevent or promote development of OS. Further, OS is only one manifestation of an entire spectrum of potential SRBD in COPD patients. Specifically, depending on the relative severity of obesity and emphysema, the patients may develop hypercapnia due to obesity hypoventilation syndrome (OHS) or sleep-related hypoventilation, respectively. Finally, patients with COPD may be at increased risk of left ventricular failure which is a known precipitant of central sleep apnea (CSA).[39] There is a paucity of literature which has examined the prevalence of CSA in COPD or OS patients.

5.1 | Clinical consequences of overlap syndrome

Both COPD and OSA can lead to respiratory and blood gas disturbances. OSA and COPD have each been individually linked with metabolic syndrome and cardiovascular morbidity.[40,41] In comparison with either OSA or COPD alone, OS patients have been found to have a worse quality of life,[42] greater nocturnal hypoxemia,[3] and a higher risk of pulmonary hypertension,[43,44] cardiovascular events,[45] and mortality.[46,47] OS patients also have higher burdens of systemic hypertension, diabetes mellitus, and obesity compared to COPD alone. OS patients have higher levels of pro-inflammatory mediators and more metabolic risk factors, and consequentially an increased susceptibility for cardiovascular disease.[48,49] In one large cohort, Kendzerska et al observed that COPD patients with nocturnal hypoxemia (who spent at least 10% of their total sleep time at an SpO_2 below 90%) were found to have increased cardiac events (myocardial infarction, stroke, congestive heart failure, revascularization, or death) compared to patients with neither COPD nor OSA.[45] In this cohort, untreated patients with COPD and severe OSA had the highest hazard; they were twice as likely to experience a cardiac event compared with patients with neither illness.

6 | CLINICAL EVALUATION FOR OVERLAP SYNDROME

OS is a treatable condition, which makes prompt diagnosis and initiation of therapy essential. Common symptoms of OSA include snoring, daytime sleepiness, nocturnal choking, and unrestful sleep. Nonetheless, the finding of daytime sleepiness is not universal, and patients may instead present with daytime fatigue.[50] Hence, questionnaires which assess sleepiness, such as the Epworth Sleepiness Scale (ESS) and the Berlin Questionnaire (BQ), may be inaccurate in predicting OSA in COPD patients.[51] Furthermore, it has been found that OSA worsens quality of life in patients with COPD even in the absence of daytime sleepiness.[42] The important physical examination findings which may suggest the possibility of OSA include obesity, increased neck circumference, and hypertension.

In a recent guideline, the American Thoracic Society (ATS) has promulgated the use of the STOPBANG (snoring, tiredness, observed apnea, high blood *p*ressure, high BMI, age, neck circumference, and male gender) questionnaire to screen for OSA in COPD patients with chronic hypercapnic respiratory failure.[52] Although direct evidence for the performance of the STOPBANG questionnaire in COPD is absent, it has been found to be the most sensitive screening tool for OSA overall with a pooled sensitivity of 0.93.[53] The utility of the STOPBANG tool has been examined in a post-hoc analysis of the Long-Term Oxygen Treatment Trial (LOTT). The LOTT failed to demonstrate benefit of long-term oxygen in COPD patients with borderline (89 – 93%), exercise-related or nocturnal hypoxemia.[54] The post-hoc analysis has revealed that in this cohort, patients with intermediate-to-high risk for OSA (STOPBANG score $\geq$3) had an increased risk for mortality, hospitalizations, and acute exacerbations.[55] This emphasizes the need for further studying the role of OSA screening and subsequent positive airway pressure (PAP) therapy in this patient population.[56]

In OSA patients, suspicion of OS should be considered in patients with significant smoking history and prominent respiratory symptoms. Patients with OS have greater nocturnal hypoxemia compared to those with OSA alone.[3] Hence, OS should be suspected in patients who require either unanticipated oxygen during PAP titration or a bilevel PAP prescription.[57] Pulmonary function testing using spirometry is required to confirm the diagnosis of COPD.

7 | DIAGNOSIS OF OVERLAP SYNDROME

There is no formal guidance for the indications of performing a sleep study in patients with COPD. Extrapolating from the ATS guidelines for hypercapnic COPD patients, it is reasonable to consider diagnostic testing in all COPD patients with an intermediate-to-high risk for OSA using the STOPBANG questionnaire.[52] Furthermore, COPD patients with pulmonary hypertension and borderline or nocturnal hypoxemia can be considered for sleep study. In-lab attended polysomnography with PAP titration is the gold standard for the diagnosis and treatment of OS. It is desirable to non-invasively record the $PaCO_2$ to capture hypoventilation events and guide PAP titration. Transcutaneous CO_2 monitoring is the preferred device for non-invasive $PaCO_2$ monitoring during sleep and unlike end-tidal CO_2 monitors, it does not impede PAP titration using a mask interface.[58]

Portable and home sleep apnea testing (HSAT) may have adequate sensitivity to diagnose OSA in COPD.[59,60] However, current guidelines recommend against use of HSAT in patients with significant chronic respiratory disease due to the following shortcomings.[61] First, HSAT is unable to identify hypoventilation as a cause for hypoxemia in these patients, which may lead to inappropriate oxygen therapy or incorrect PAP prescription. Secondly, HSAT is often combined with auto-PAP therapy. This may be followed by an inappropriate increase in expiratory positive airway pressure (EPAP) level which can worsen hyperinflation and lung function in COPD (see below).[62,63] The use of newer algorithms for auto-titrating PAP therapy in OS remains an area of active research.[64]

8 | PHYSIOLOGICAL BASIS OF POSITIVE AIRWAY PRESSURE (PAP) THERAPY

PAP therapy delivered via a mask interface is a non-invasive externally applied pressure on the patient's airway. The two common modes of PAP used in OS are CPAP and bilevel positive airway pressure (BPAP). In CPAP, a constant pressure is applied which mechanically splints open the patient's upper airway and thereby prevents its collapse. It is the most common mode of PAP used for the therapy of OSA.[65] BPAP employs two different levels of PAP during the breathing cycle: a higher level during inspiration, that is, the inspiratory PAP (IPAP); and a lower level during expiration, i.e., the expiratory PAP (EPAP). The difference between the IPAP and the EPAP supports the patient's inspiration by augmenting the tidal volume and providing rest to the respiratory muscles.[65] Hence, BPAP is a form of non-invasive ventilation (NIV). It is particularly useful in patients with hypoventilation due to overloaded respiratory muscles. The choice between CPAP and BPAP therapy can be illustrated with the example of OHS. Herein, randomized controlled trial (RCT) data has shown that patients with coexistent severe OSA (AHI >30 events/hour) derive similar benefit from CPAP and BPAP

because the upper airway obstruction is the dominant pathophysiological abnormality and is corrected with CPAP.[66] Contrarily, in OHS patients without severe OSA, hypoventilation is the dominant abnormality, and hence BPAP has been employed successfully to improve blood gases, sleepiness, and quality of life.[67] On occasion, CPAP failure in OHS with severe OSA may also require use of BPAP therapy.

The use of PAP therapy in patients with COPD requires two important considerations. First, patients with emphysema phenotype suffer from expiratory airflow limitation, air trapping, and hyperinflation. This results in an inward chest recoil pressure at the end of expiration. This is known as the intrinsic or auto-positive end expiratory pressure (auto-PEEP).[68] Consequently, the patient needs to overcome the auto-PEEP prior to each inspiration. In the awake state, patients adapt using pursed lip breathing and prolonged expiration to minimize auto-PEEP.[69] However, during sleep the expiratory time is shortened leading to dynamic hyperinflation. The use of modest amounts of applied PEEP in the form of CPAP or EPAP may negate the auto-PEEP, support ventilation and reduce muscle fatigue. CPAP of 8 cm H_2O has been shown to reduce hyperinflation in stable COPD.[70] However, if the applied PEEP is more than the auto-PEEP, it may impose an additional expiratory load, thereby deterring ventilation. CPAP greater than 10 cm H_2O may worsen hyperinflation.[62,63] In a study of OS patients, use of mean CPAP pressure of 11 cm H_2O resulted in worsening of lung function.[31]

Secondly, patients with emphysema-predominant COPD may have a downward displaced diaphragm which is mechanically disadvantaged. When combined with accessory muscle paralysis in REM sleep, this may result in sleep-related hypoventilation.[71] Such patients may have poor sleep quality with daytime fatigue and chronic hypercapnia. COPD patients with chronic hypercapnic respiratory failure are at increased risk of mortality. Often, these patients do not have OSA as defined by the AHI cut off because of the protective influence of emphysema on upper airway collapsibility.[34] Hence, CPAP may not be useful in this phenotype. Rather, the use of BPAP, which supports ventilation in these patients, may reduce risk of mortality and hospitalizations with improved dyspnea and quality of life.[52] Recently, trials have used high IPAP settings in these patients with a back-up respiratory rate to achieve greater minute ventilation with an aim to normalize the $PaCO_2$. This approach, termed as high-intensity NIV has been shown to improve blood gases in physiological studies and is under further investigation.[72-74]

9 | EVIDENCE FOR THE USE OF PAP THERAPY IN OVERLAP SYNDROME

To date, only observational studies of PAP therapy in OS patients have been conducted. PAP therapy in OS patients has been found to reduce pro-inflammatory markers implicated in cardiovascular disease, including C-reactive protein (CRP) and tumor necrosis factor-α.[75,76] has been linked with physiological benefits in OS including improved arterial blood gases (reduced $PaCO_2$ and increased PaO_2),[28,32,77] 6-minute walk distance,[78] forced expiratory volume in 1 s (FEV_1),[32,79] respiratory muscle strength,[80] skeletal muscle strength,[80] exercise capacity,[80] and mean pulmonary artery pressure.[81]

Patients who are adherent to PAP therapy have been found to have reduced COPD exacerbations,[82] COPD-related hospitalizations,[46,83,84] cardiovascular events,[45] and mortality.[46,82,85,86] Most of these studies employed CPAP. Patients with emphysema have been found to have lower CPAP adherence compared with obese patients with daytime sleepiness.[87]

OS is amenable to phenotyping. Figure 1 shows that patients with COPD may suffer from a spectrum of SRBD, the exact nature of which depends on the relative severity of the emphysema and obesity. Patients with emphysema have higher sleep-related hypoventilation due to the mechanically disadvantaged downwardly displaced diaphragm, but they are protected against OSA because of low BMI and caudal traction on the upper airways. In contrast, patients with

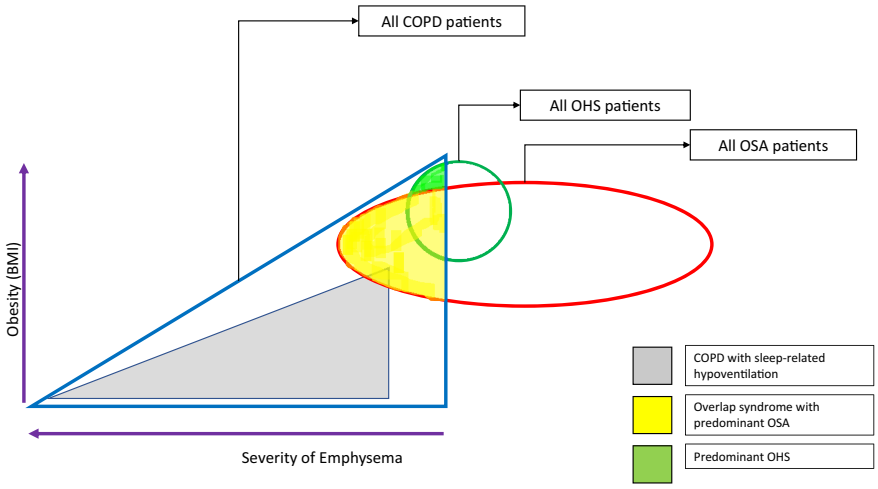

FIGURE 1 Proposed phenotypic classification of sleep-related breathing disorders in Chronic Obstructive Pulmonary Disease. BMI, body mass index, COPD, chronic obstructive pulmonary disease, OSA, obstructive sleep apnea, OHS, obesity hypoventilation syndrome.

obesity tend to have predominant OSA or OHS. Not shown in the figure, patient may also have co-existent CSA, especially if there is co-existent heart failure or opioid use. This figure is not to exact scale as the epidemiological studies of relative frequencies of different phenotypes have not been performed.

Currently, there is no formal guidance for the use of PAP therapy in patients with COPD and SRBD. In the absence of well-designed RCTs, our understanding is limited to large observational studies and extrapolations of evidence from related conditions such as OSA, COPD with chronic hypercapnia and OHS. We have presented a decision-tree of a proposed phenotype-based management algorithm of SRBD in COPD (Figure 2).

Figure 2 shows that, in patients of COPD with suspected SRBD, the decision for performing an in-lab

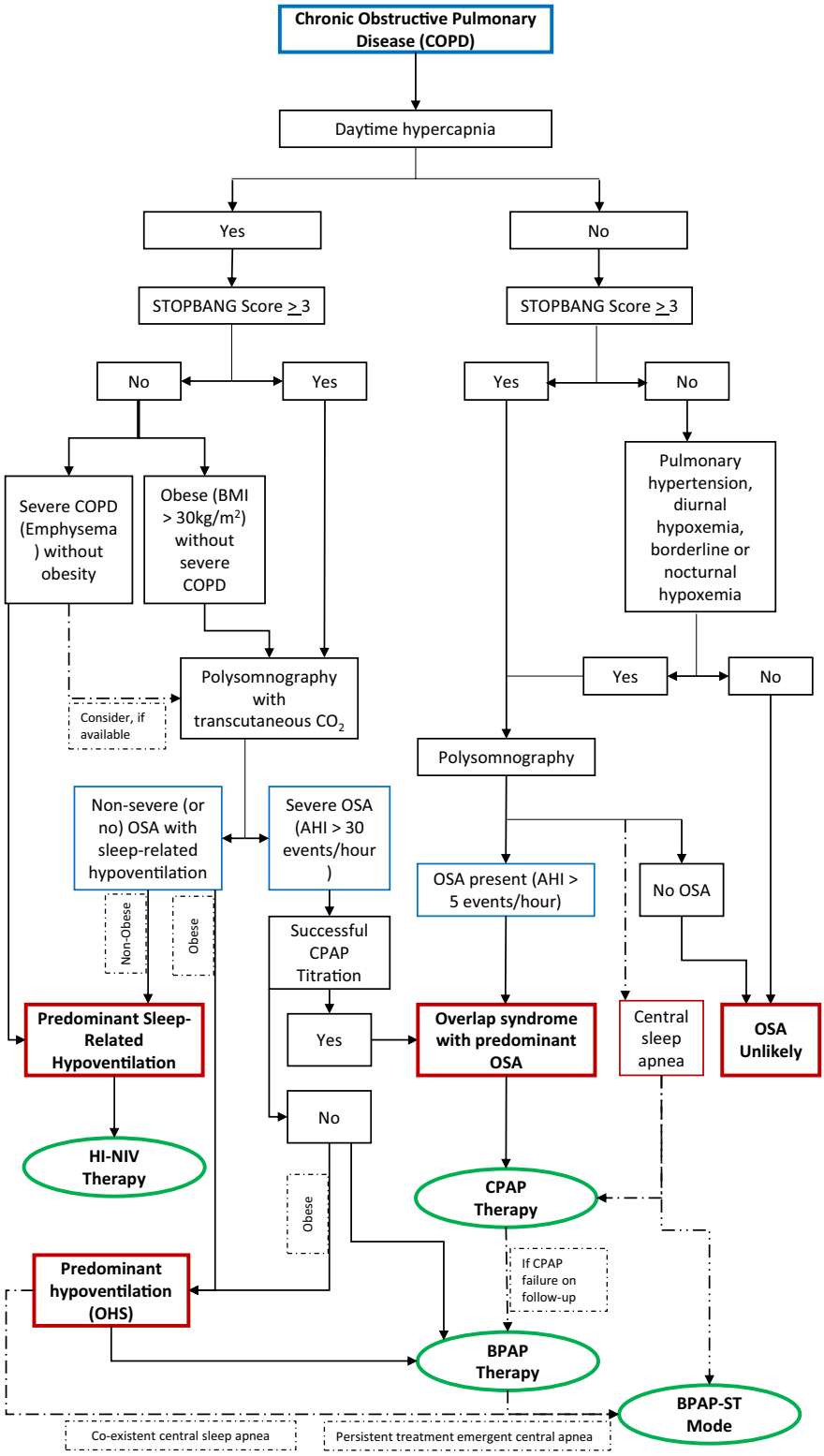

FIGURE 2 A phenotype-guided approach toward the diagnosis and positive airway pressure therapy of sleep-related breathing disorders with Chronic Obstructive Pulmonary Disease. BMI, body mass index; BPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; high blood pressure, high BMI, age, neck circumference and male gender; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; STOPBANG, snoring, tiredness, observed apnea.

polysomnography depends on the presence of diurnal hypercapnia, risk for OSA (e.g., STOPBANG questionnaire), and pulmonary hypertension. In addition, patients with borderline or nocturnal hypoxemia may be potential candidates for diagnostic testing. Polysomnography can help in identifying the presence and the phenotype of SRBD in COPD patients. The choice between CPAP, BPAP or high-intensity NIV depends on whether the predominant phenotype is OSA, OHS, or sleep-related hypoventilation due to COPD, respectively. Additionally, the patient may have co-existent CSA, especially if they have comorbid heart failure or opioid use. The use of CPAP or BPAP with ST mode may be considered for CSA.

10 | OTHER THERAPIES FOR OVERLAP SYNDROME

10.1 | Oxygen therapy

PAP therapy in OS has been shown to increase daytime oxygen saturation and may obviate need for oxygen in patients with borderline hypoxemia.[32,77,79] As a corollary, inappropriate long-term oxygen therapy in patients with borderline hypoxemia and OS may increase mortality, hospitalizations, and acute exacerbations.[55] Supplementary oxygen therapy (with target SpO_2 of 88 – 92%) should be considered in patients with OS who continue to have hypoxemia despite PAP therapy. However, in this situation, presence of hypoventilation during titration study may aid in choosing BPAP therapy over supplementary oxygen. However, head-to-head comparisons of BPAP versus CPAP with supplementary oxygen have not been made.[88]

10.2 | Pharmacological therapy

The use of PAP therapy in OS has not been shown to reduce the need for bronchodilators in COPD.[89] Long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) should be continued as per COPD management guidelines. Both LABA and LAMA have been shown to increase nocturnal oxygen saturation without improving sleep quality.[90,91] The impact of inhaled corticosteroids (ICS) is more contentious. One study has shown that ICS may improve AHI, nocturnal hypoxemia, daytime PaCO2, and lung function via airway anti-inflammatory effects.[92] However, others have suggested that ICS may predispose to myopathy which may worsen upper airway collapsibility leading to OSA.[88] Further, ICS is neither used as monotherapy nor as a first-line therapy in COPD.[84] Hence, the effects of ICS in OS need to be further studied before any conclusion may be drawn. The use of sedatives and opioids should be avoided in COPD patients due to the risk of worsening central hypoventilation or CSA.[93] There are no studies examining the use of respiratory stimulants such as acetazolamide in OS. Their use has been shown to improve oxygenation without benefit in clinical outcomes in COPD. Further, acetazolamide may potentially cause harm (e.g., worsening respiratory acidosis in severe COPD).[94] Hence, respiratory stimulants are not currently recommended in OS.

11 | RECENT TRENDS AND FUTURE DIRECTIONS

The current definition of OS is restrictive and fails to acknowledge the entire spectrum of sleep-disordered breathing which may be encountered in patients with COPD. No studies to date have examined the occurrence of CSA in COPD patients despite plausible pathophysiological links.[95] Hence, it is imperative to conduct studies to characterize the prevalence of OSA, CSA, OHS, and pure hypoventilation related to COPD in this population. This will enable us to design trials for phenotype-directed therapeutic modes of PAP therapy. Furthermore, the role of in-lab polysomnography for NIV titration in COPD patients with chronic hypercapnic respiratory failure needs to be further examined.[52]

Although PAP therapy is currently the standard therapy for OS, there are no clinical trials which have examined its effects on clinical outcomes in this population. An ongoing trial is examining the effect of non-invasive ventilation in overlap syndrome (NCT03184714). A randomized trial is studying the impact of early diagnosis and treatment of OSA in COPD patients requiring hospitalizations in preventing readmission (NCT03647462). Another randomized trial is comparing the effect of CPAP and BPAP therapy in correcting blood gases in hypercapnic OS patients (NCT03766542). A randomized trial is studying the non-inferiority of home-initiation of NIV versus hospitalized titration in OS (NCT02363413). Once the results of these trials are available, they will shed light on important aspects of PAP therapy for OS.

In the recent INOX trial, the application of nocturnal oxygen failed to reduce mortality or progression to long-term oxygen therapy in COPD patients with nocturnal hypoxemia.[96] However, the presence of sleep-related hypoventilation in such patients cannot be excluded. Hence, the role of diagnosis and therapy of SRBD in COPD patients with borderline and nocturnal hypoxemia is another potential research area.

Finally, newer modes of non-invasive ventilation need to be studied in OS. Volume-assured pressure support (VAPS) with fixed or auto-EPAP has been found to be effective in chronic hypoventilation in COPD patients in small studies.[97] It has potential to assure adequate minute ventilation despite varying ventilatory drive and patient effort in different stages and postures of sleep. A novel non-invasive mode specifically tailored for OS is the auto-trilevel PAP. This mode

employs a lower EPAP at beginning of expiration to counteract auto-PEEP without causing dynamic hyperinflation. It uses a higher EPAP at end expiration, when upper airway collapsibility is most likely. In a pilot physiological study, it was superior to BPAP in improving AHI, nocturnal hypoxemia, sleep efficiency and daytime sleepiness.[98]

12 | CONCLUSION

Sleep leads to changes in the respiratory function which bear no adverse impact on a healthy person but may be detrimental to patients with underlying respiratory diseases such as COPD. OSA and COPD are on the rise globally, and their co-existence as OS can impair quality of life, worsen respiratory failure, and increase risk of pulmonary hypertension, cardiovascular events, or death compared to either disease alone. Further, COPD may be associated with a spectrum of SRBD including sleep-related hypoventilation and CSA. Diagnosis requires high index of suspicion and an in-lab polysomnography. A phenotype-based approach of selecting PAP therapy which is tailored to correct the pathophysiology of SRBD demonstrates potential to improve clinical outcomes. To strengthen the evidence base, additional research is needed in the form of well-designed clinical trials which use the phenotypic approach to the management of OS and SRBD in COPD.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

TMS and JCS designed the review, wrote, and edited the manuscript.

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