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Chronic obstructive pulmonary disease and obstructive sleep apnea overlap: who to treat and how?

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Abstract

Introduction: The co-existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), or the overlap syndrome, is common and associated with a distinct pattern of nocturnal hypoxemia and worse clinical outcomes than either disease alone. Consequently, identifying who and how to treat these patients is essential.

Areas covered: Treatment is recommended in all patients with OSA and symptoms or systemic hypertension, but determining symptoms attributable to OSA can be challenging in patients with COPD. Treatment should be considered in asymptomatic patients with moderate to severe OSA and COPD with pulmonary hypertension and comorbid cardiovascular and cerebrovascular disease, especially if marked hypoxic burden. CPAP is effective, but in patients with the overlap syndrome and daytime hypercapnia, high-intensity noninvasive ventilation aiming to lower $PaCO_2$ may have additional benefits. Additionally, in those with severe resting daytime hypoxemia, supplemental oxygen improves survival and should be added to positive airway pressure. The role of alternative non-positive airway pressure therapies in the overlap syndrome needs further study.

Expert opinion: Both COPD and OSA are heterogeneous disorders with a wide range of disease severity and further research is needed to better characterize and prognosticate patients with the overlap syndrome to personalize treatment.

Keywords

Overlap syndrome; obstructive sleep apnea; chronic obstructive pulmonary disease; noninvasive ventilation; obstructive lung disease

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1. Introduction

In 1985, David Flenley recognized the co-existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) was associated with a distinct pattern of nocturnal hypoxemia with therapeutic implications (see Figure 1) [1]. Coined the overlap syndrome, mounting evidence has since associated it with worse clinical outcomes than either COPD or OSA alone.

Both COPD and OSA are common affecting about 10% of adults and prevalence is only expected to increase [2–5]. Yet, prevalence studies on the overlap syndrome have reported variable results, estimated at 1% in the general adult population [6–18]. This reported variability is likely in part due to the heterogeneity of both COPD and OSA.

A spectrum of disease phenotypes and severity is seen for both COPD and OSA limiting generalized statements regarding treatment for the overlap syndrome. However, given the morbidity and mortality associated with the overlap syndrome, understanding how best to treat these patients is essential. This review aims to cover who and how to treat these patients, highlighting the pressing need to define and characterize this heterogeneous disorder better to personalize treatment.

2. Whom to treat

Deciding who to treat requires an understanding of the consequences of untreated disease and the benefits and risks of treatment. A comprehensive discussion regarding the management of COPD itself is beyond the scope of this review and instead we focus on the treatment of sleep disordered breathing in COPD.

2.1. Whom with OSA alone to treat

OSA when untreated can be associated with various symptoms, although many are subtle and may be minimally evident or underreported. Excessive sleepiness is reported in 15–50% of patients with OSA identified through general population screening [19]. Patients may also complain of fatigue, feeling tired, lack of energy, nocturnal gasping or choking and/or symptoms of insomnia. OSA is also associated with reduced quality of life and multiple adverse clinical consequences including a 2- to 3-fold increased risk of motor vehicle accidents, systemic hypertension, stroke, atrial fibrillation, congestive heart failure, coronary heart disease, type 2 diabetes mellitus, impaired cognition, and increased mortality [20–26]. Evaluating who with OSA to treat requires a comprehensive evaluation of these symptoms, medical comorbidities, and high-risk occupations, but also an understanding of the potential benefits and risks of therapeutic options.

Continuous positive airway pressure (CPAP) is the mainstay of treatment for OSA. A systematic review conducted by the American Academy of Sleep Medicine (AASM) demonstrated that CPAP compared to no treatment results in a clinically significant reduction in disease severity across the spectrum of OSA severity [20]. The Epworth Sleepiness Scale (ESS) is the most commonly used subjective measure of sleepiness and CPAP has been associated with an approximate −2.4 points reduction in ESS in OSA [20].

CPAP has also been shown to improve sleep-related quality of life, and based on their review of the evidence, the AASM published clinical practice guidelines recommending treatment of all sleepy patients and most patients with reduced sleep-related quality of life with OSA, regardless of disease severity [27].

However, we and others have shown that symptoms other than sleepiness are not uncommon in OSA [28,29]. Ronald Chervin explored preferred terms used to describe OSA symptoms in a clinical sample of patients with severe OSA and found fatigue, tiredness, and lack of energy were reported more frequently than sleepiness [28,29]. Symptom description may also vary between gender. We found females and older patients with OSA were significantly less likely to report sleepiness using an ESS ≥ 10 [29]. Similarly, in the Sleep Heart Health Study, a multicenter cohort study designed to determine the cardiovascular consequences of OSA, Baldwin et al. found men and women answered questions on sleepiness differently [30]. Women reported feeling sleepy as often as men did, but women were less likely to have an ESS ≥ 10 and were more likely to report feeling unrested than men. Consequently, reliance on the ESS alone in identifying these paucisymptomatic patients to determine treatment decisions in OSA has potential limitations, especially in women.

The benefits of CPAP in asymptomatic patients are less clear. Available evidence has not demonstrated a clear association between mild OSA, typically defined as an AHI < 15 events per hour, with increased cardiovascular or cerebrovascular events including cardiovascular or all cause-mortality [31].Not surprisingly, there is limited or inconsistent evidence pertaining to the impact of therapy of mild OSA on cardiovascular events, stroke, arrhythmias, and neurocognition. Thus, routine use of CPAP in mild asymptomatic OSA cannot be recommended [31].

When compared to mild OSA, in patients with asymptomatic OSA of greater disease severity based on AHI, the role of CPAP is more controversial. CPAP has been shown to improve BP control in moderate to severe OSA, including small but clinically relevant reductions in nighttime and daytime systolic and diastolic BP and 24 hour BP [20]. Observational studies, often comparing CPAP adherent to non-adherent groups, have also suggested improvements in cardiovascular events with CPAP use, but these benefits have not been substantiated by randomized trials [32–35]. These randomized trials have been criticized for exclusion of sleepy patients and poor CPAP adherence, but no improvements in composite cardiovascular events, including rates of myocardial infarction, stroke or mortality, have been shown with CPAP, as both primary and secondary prevention. The Sleep Apnea Cardiovascular Endpoints (SAVE) study was a larger multicenter randomized clinical trial of over 2700 adults with moderate to severe OSA and coronary or cerebrovascular disease randomized to usual care or usual care plus CPAP [32]. After a mean follow-up of 3.7 years, there was no significant difference in the primary composite end point of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack, despite improvements in daytime sleepiness and health-related quality of life with CPAP. Again, this study excluded patients with severe daytime sleepiness based on an ESS > 15, but it also excluded patients with very severe hypoxemia defined using an oxygenation saturation < 80% for > 10% of recording time, which may be of relevance in patients with COPD,

as discussed below. Similarly the data on CPAP in atrial fibrillation and arrhythmias in OSA have been mixed. While small observational studies have supported reduced atrial fibrillation burden with CPAP use following ablation or cardioversion, in a randomized trial of 108 adults with paroxysmal atrial fibrillation and moderate to severe OSA randomized to 5 months of CPAP plus usual care or usual care alone, CPAP did not result in a significant reduction in the burden of atrial fibrillation as measured by implantable loop recorder [36]. CPAP has also not been shown to improve neurocognitive function in adults or reduce fasting glucose or $HbA1_C$ in adults with OSA with or without type 2 diabetes mellitus [20].

Knowing these potential benefits of CPAP, a summary of who with OSA to treat is shown in Table 1. This summary largely reflects the AASM clinical practice guidelines recommending a trial of CPAP in all sleepy patients, patients with reduced sleep-related quality of life, and those with high-risk occupations or who have had a motor vehicle accident with OSA of any severity. The AASM suggests CPAP to treat OSA in patients with comorbid hypertension but concluded that there was insufficient or inconclusive evidence to either recommend or withhold PAP to treat non-sleepy adults with OSA as a means to reduce cardiovascular events or mortality. An informed decision weighing the potential benefits and risks of CPAP is recommended in asymptomatic patients with more moderate to severe OSA, especially given the few side effects described with CPAP.

The benefits of CPAP are directly correlated with adherence and given some of the challenges with adherence with CPAP, there has been, and is, ongoing research looking at alternative therapeutic options for OSA. Again, identifying who with OSA to treat with these alternative therapies requires an understanding of the potential benefits and risks of these treatments. Of the alternative therapeutic options, most evidence exists for oral appliances. Custom, titratable oral appliances are less efficacious than CPAP in reducing the AHI but have been shown to be equivalent to CPAP in reducing subjective daytime sleepiness, mainly among patients with more severe OSA [37]. Oral appliances have also been shown to be near equivalent to CPAP for improving sleep-related quality of life and reducing BP in OSA, but data on their impact on other cardiovascular outcomes are lacking [37]. Similarly, hypoglossal nerve stimulation is a newer treatment option that involves implantation of a neurostimulator in the chest wall and an electrode on a branch of the hypoglossal nerve to enhance tongue protrusion. It too has been shown to improve the AHI in select patients with moderate to severe OSA, but, like the oral appliance, their efficacy in patients with the overlap syndrome is unknown [38–40].

2.2. Whom with overlap syndrome to treat

There is no reason to think that the indications for treating OSA are different in patients with COPD or the overlap syndrome, but there are some unique considerations when deciding who with OSA to treat in patients with co-existing pulmonary disease.

i. Firstly, teasing out symptoms attributable to OSA in COPD can be challenging. Sleep-related complaints, in terms of both sleep quantity and quality, are common in COPD [6,41–46]. These complaints include difficulties falling asleep, staying asleep, early awakenings and non-restorative sleep, fatigue, and excessive sleepiness; sleep difficulties ranked third after dyspnea and fatigue

in 146 patients with COPD asked to rate the frequency of occurrence of 11 symptom categories [47]. Multiple factors contribute to these complaints of poor sleep in COPD, including the symptoms of COPD themselves, smoking or nicotine withdrawal, physical inactivity, hypoxemia, work of breathing, medications used in the treatment of COPD, and medical co-morbidities like depression and anxiety. Determining which sleep-related complaints are explained by OSA can be a challenge, but currently there is emphasis placed on symptoms, especially sleepiness, in deciding which patients with OSA to treat.

ii. The normal stage specific changes in respiration that occur during sleep result in more pronounced sleep hypoxemia and hypercapnia in patients with COPD with altered respiratory mechanics and gas exchange abnormalities. Nocturnal oxygen desaturation is common in COPD, especially during REM sleep [1,7,11,12,48]. This notion has implications in our current diagnostic criteria for OSA which has direct therapeutic implications. Currently, diagnosis of OSA relies on a single metric, the apnea-hypopnea index, which relies on the consequences of oxygen desaturation and arousals. However, in patients with COPD with baseline hypoxemia who lie on the steep portion of the oxyhemoglobin desaturation curve, oxygen desaturation can occur more readily in the presence of airway obstruction potentially overdiagnosing OSA. Conversely, OSA may be underdiagnosed in patients with COPD on supplemental oxygen by abolishing desaturations. Defining the optimal diagnostic criteria for OSA in COPD is essential given our current reliance on the AHI in determining who to treat [10].

iii. The overlap syndrome is associated with worse clinical outcomes including mortality than either COPD or OSA alone [1,7,11,12,15,48–50]. Marin et al. compared patients with the overlap syndrome treated with CPAP to patients with untreated overlap syndrome and patients with COPD alone, all free of heart failure, myocardial infarction, or stroke, followed for a median of 9.4 years [51]. Patients with untreated overlap syndrome had higher mortality (relative risk 1.79; 95% confidence interval 1.16–2.77) and were more likely to suffer a COPD exacerbation leading to hospitalization (relative risk 1.70; 95% confidence interval 1.21–2.38) than patients with COPD alone. When treated with CPAP, this risk was reduced, although this was an observational study implicating association only. Stanchina et al. also demonstrated a dose response CPAP effect on mortality in the overlap syndrome [52].

The leading cause of death in Marin’s study was cardiovascular events. In a meta-analysis comparing cardiovascular and cerebrovascular comorbidities between the overlap syndrome and patients with COPD or OSA, the overlap syndrome significantly increased risk of developing hypertension and pulmonary hypertension compared with COPD and OSA, but there was no significant difference in the prevalence of coronary heart disease and cerebrovascular disease between patients with the overlap syndrome and COPD [53]. Both COPD and OSA have been associated with cardiovascular disease, and the relationship is complex with shared pathophysiological mechanisms including inflammation, endothelial dysfunction, and oxidative stress.

There may be an association between hypoxic burden in OSA and cardiovascular events [54]. In COPD alone, nocturnal oxygen desaturation has been associated with pulmonary hypertension, cardiac arrhythmias and worse clinical outcomes [55–58]. Fletcher et al. retrospectively examined survival in 169 patients with COPD with daytime PaO_2 ≥60 mm Hg with and without NOD [59]. Survival corrected for age was significantly better in COPD subjects without NOD, but correction of NOD with supplemental oxygen did not result in a statistically significant survival benefit. The precise mechanistic contribution of sleep hypoxemia burden in the overlap syndrome on cardiovascular disease is unclear. Furthermore, a signal for greater cardiovascular benefits with CPAP has been shown in patients with OSA with high hypoxemic burden. The Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAAC) study was a randomized clinical trial that, like the SAVE study, failed to demonstrate reductions in cardiovascular effects with CPAP use in non-sleepy patients with acute coronary syndrome diagnosed with moderate to severe OSA, but a post-hoc analysis found that in patients with high hypoxic burden, CPAP treatment was associated with a significant reduction in the incidence of cardiovascular events, while the low hypoxemic burden group exhibited a trend toward a higher risk of cardiovascular outcomes compared to untreated patients [60]. Again, patients with the overlap syndrome have greater hypoxic burden than either OSA or COPD alone, and while the study by Marin et al. supported lower mortality with CPAP use in the overlap syndrome, currently no randomized clinical trials have investigated CPAP on cardiovascular risk and mortality specifically in the overlap syndrome. Until further studies are available, we suggest a comprehensive discussion with the patient regarding the potential benefits and risks of treatment in asymptomatic patients with the overlap syndrome and pulmonary hypertension and/or cardiovascular disease, especially if high hypoxic burden.

iv. As mentioned, both COPD and OSA are very heterogeneous disorders with a wide range of severities. Celli et al. recently proposed revising the definition and taxonomy of COPD as a clinical syndrome to better reflect disease heterogeneity [61,62]. It is unclear what combination of disease phenotype and severity are associated with the adverse clinical outcomes described in the overlap syndrome. A patient with mild OSA based on AHI and emphysema with a severely decreased FEV_1 and a patient with severe OSA based on an AHI but chronic bronchitis and mild COPD based on FEV_1 both meet the current definition of the overlap syndrome, but the two patients are likely to have differing patterns of both awake and nocturnal oxygenation and clinical manifestations including cardiovascular complications. This heterogeneity was even described in Flenley's original description where he pointed out the overlap between OSA and the 'blue and bloated' phenotype of COPD yielded more profound sleep hypoxemia compared to the overlap between OSA and the 'pink and puffing' phenotype of COPD and other pulmonary disorders [1]. Additional research is needed to understand better the risk factors for the development of symptoms and clinical

consequences across the spectrum of overlap syndrome heterogeneity to better identify who to treat.

A summary of who to consider OSA treatment for in patients with the overlap syndrome is provided in Table 1. A visual treatment algorithm is provided in Figure 2.

3. How to treat

Treating the overlap syndrome is currently directed at individually treating COPD and OSA, but again much of the focus of this review is on OSA treatment.

As discussed, CPAP is very effective, and again the first line treatment for most patients with moderate to severe OSA. It can be initiated either in the home setting, typically using an auto-adjusting CPAP (APAP) unit, or in the sleep laboratory following split-night or full-night titration polysomnography. Studies comparing initiation of APAP vs in-laboratory PAP titration, however, generally exclude patients with significant pulmonary disease including COPD. Again patients with the overlap syndrome are susceptible to greater sleep hypoxemia and hypercapnia, and in-laboratory titration is recommended to determine optimal treatment settings, especially in patients requiring supplemental oxygen [63]. The availability of transcutaneous CO_2 monitoring may allow for more sophisticated titration of optimal positive airway pressure settings, but this is an area needing further research, especially given increasing challenges with access to sleep laboratories.

A subset of patients with the overlap syndrome may benefit more from bilevel positive airway pressure (BPAP) or noninvasive positive pressure ventilation (NIV) compared to CPAP or APAP. Bilevel positive airway pressure has been shown to have similar effects on residual AHI, clinical outcomes, and adherence compared with standard continuous positive airway pressure in OSA [20]. In chronic stable COPD, the data on NIV have been mixed, but a systematic review and individual patient data meta-analysis by Struik et al. investigating the effects of NIV in patients with stable COPD found significant differences in change in $PaCO_2$ between NIV and control groups in patients with higher baseline $PaCO_2$ of at least 55 mm Hg, better adherence, and higher inspiratory positive airway pressure of at least 18 cm H2O compared to controls [64]. Subsequent randomized controlled trials in the subset of COPD patients with hypercapnia when employing a ‘high intensity’ mode of NIV have shown improvements in gas exchange, dyspnea, exercise tolerance, health-related quality of life, and possibly reductions in mortality and hospitalizations [65–71]. High-intensity NIV refers to use of high inspiratory pressures and a high backup rate to target normalization of $PaCO_2$. Kohnlein et al. randomized close to 200 patients with severe COPD and stable hypercapnia ($PaCO_2$ ≥51.9 mmHg during wakefulness) to NIV delivered to target reductions in baseline $PaCO_2$ by at least ≥ 20% or values <48 mm Hg or optimized standard care [69]. NIV improved survival with a 1-year all-cause mortality of 12% compared to 33% in the control group. Based on more recent evidence, updated American and European clinical guidelines now suggest use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD. While there are currently no randomized clinical trials comparing BPAP to CPAP in the overlap syndrome, we recommend considering BPAP when initiating treatment for OSA in patients with the overlap syndrome with baseline

hypercapnia, especially if recurrent COPD exacerbations, using a high pressure support and backup rate to try and correct $PaCO_2$ [65,68,71].

Unfortunately, in the United States, despite growing evidence supporting NIV use in stable hypercapnic COPD patients, initiation of NIV, especially with a backup rate, is limited by the current onerous reimbursement criteria by the Centers for Medicare and Medicaid Services (CMS) and payers for bilevel positive airway pressure devices. Volume targeted pressure support modes including average volume assure pressure support (AVAPS) and intelligent volume assured pressure support (iVAPS) use proprietary algorithms to adjust pressure support within a set range to achieve a target tidal volume (AVAPS) or estimated alveolar ventilation (iVAPS) respectively. In COPD, volume-targeted pressure support appears to be at least as effective as fixed pressure support, but no clear superiority in oxygenation, exercise capacity, health-related quality of life, self-reported comfort or adherence has been shown, especially long term [65,72–75]. Some home ventilators now also have the added option of auto-titrating expiratory positive airway pressure to target upper airway obstructive events, much like auto-CPAP, opening the door for patients with the overlap syndrome. In a randomized, double-blind, cross-over study of 25 patients with chronic hypoventilation and OSA, 9 with COPD, iVAPS with autoEPAP was comparable to fixed EPAP in controlling OSA over 2 separate nights of attended PSG [76]. Further studies are needed to determine the role of volume-targeted pressure support modes, especially with auto-EPAP in the overlap syndrome, but McDowell et al. demonstrated feasibility of remote monitored home iVAPS-autoEPAP in patients with COPD, including a small subset with co-existing OSA [77].

In patients with the overlap syndrome a further consideration is supplemental oxygen. Supplemental oxygen alone is not recommended for treating OSA. While supplemental oxygen will improve measures of oxygenation, it can prolong the duration of obstructive apneas and is inferior to CPAP in reducing the AHI [78–80]. In COPD, long-term oxygen (≥15 hours per day) has been shown to improve survival in patients with severe resting hypoxemia [81–83]. The inclusion criteria of the Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council (MRC) showing these survival benefits continue to be the basis of the current CMS criteria for oxygen reimbursement in the United States: PaO_2 ≤55 mm Hg or SpO_2 ≤88% or PaO_2 56–59 mm Hg or SpO_2 of 89% if evidence of dependent edema suggesting congestive heart failure, pulmonary hypertension, or cor pulmonale or erythrocytosis. We recommend continued use of supplemental oxygen with CPAP in patients with the overlap syndrome who meet current resting hypoxemia criteria for supplemental oxygen use in COPD. Typically supplemental oxygen is delivered using an oxygen adapter connected in line with the positive airway pressure interface and tubing, although for COPD patients with high oxygen flow requirements >4 L/min, reliable FiO_2 delivery becomes more limited. Moreover, in patients with COPD meeting criteria for supplemental oxygen, oxygen requirements are typically higher in sleep. Mulloy et al. studied ventilation and gas exchange in 19 patients with severe stable COPD during sleep and incremental treadmill exercise and found oxygen saturation fell twice as much during sleep as during maximum exercise: 13.1(8.9) vs 6.0(3.6) % ($p < 0.001$) [84].

Similar survival benefits with supplemental oxygen have not been shown in patients with COPD and less severe hypoxemia including isolated sleep hypoxemia [85–88]. The International Nocturnal Oxygen (INOX) study was a randomized, placebo-controlled trial designed to study the effects of nocturnal oxygen on mortality or worsening of disease in COPD patients with nocturnal oxygen desaturation that did not meet criteria for long-term oxygen [87]. The study, however, was stopped prematurely due to difficulties with recruitment and retention, and to date no survival benefit has been shown for nocturnal oxygen in isolated sleep hypoxemia. Despite this, it is our experience that patients with COPD are often prescribed supplemental oxygen for isolated exertional and/or sleep hypoxemia. In patients with the overlap syndrome, there should be caution using supplemental oxygen alone given the potential for worsening hypercapnia. Alford et al. looked at the effects of acute oxygen in 20 males with the overlap syndrome by completing successive polysomnographies on room air and on nocturnal oxygen at 4 L/min for one night each [89]. Nocturnal oxygen improved oxygenation but significantly prolonged apnea and hypopnea event duration and increased end apneic PCO_2. Consequently, supplemental oxygen can only be recommended in the overlap syndrome in conjunction with positive airway pressure when severe daytime resting hypoxemia.

High flow nasal cannula (HFNC) is a modality of oxygen and pressure delivery commonly used in the acute setting for patients with respiratory failure. The role for HFNC specifically in overlap syndrome is not solidified by current evidence. This modality delivers high levels of air and/or oxygen up to 60 L/minute by some devices. The high volumes delivered at the nasopharynx fill the pharynx and trachea with oxygen and help to scrub carbon dioxide which has been expelled there without respiratory effort by the patient. HFNC effectively reduces anatomical dead space, allowing the patient reduced work of breathing and ventilatory burden. While there likely is some benefit to augmenting ventilation in overlap syndrome given baseline respiratory failure in these patients, HFNC has not performed as well as traditional positive pressure modalities in albeit limited clinical trials. We suspect HFNC performs less well in patients with concomitant OSA given a reduced ability to overcome upper and lower airway resistance when compared to a true pressure targeted modality [90–94].

There are very little data on the role of non-positive airway pressure therapies in the overlap syndrome. The benefits and risks of oral appliances and hypoglossal nerve stimulation in the overlap syndrome remain unknown, with most studies on alternative therapies excluding patients with significant pulmonary disease.

While the focus has been on the treatment of OSA in the overlap syndrome, few studies have explored the impact of COPD treatment on sleep disordered breathing and clinical outcomes in the overlap syndrome. Bronchodilators including long-acting muscarinic antagonist and long-acting β_2-agonist therapy have been shown to improve sleep oxygenation in patients with COPD, possibly decreasing supplemental oxygen needs during sleep, without consistent improvements in sleep quality [95,96]. The effects of COPD therapies on OSA are yet unknown, but standard pharmacologic and non-pharmacologic therapies for COPD, guided by severity of airflow obstruction, symptoms, exacerbation risk, and co-morbidities, are recommended for patients with overlap syndrome, just like any other patient with COPD.

3.1. Treatment in the acute setting

Treatment of acute decompensated overlap syndrome generally follows the guidelines of management of acute COPD exacerbations. If hypercapnia or excessive work of breathing is present, acute NIV may be needed to assist with ventilation. In some severe cases without adequate response to initial treatment, respiratory failure may progress to need for invasive ventilation. Caution should be taken to avoid air trapping which can cause life-threatening hemodynamic instability in patients with COPD and severe lower airway obstruction. However, adequate expiratory positive airway pressure is needed to overcome upper airway obstruction in the overlap syndrome. Consequently, in patients with the overlap syndrome undergoing NIV in the acute setting we emphasize titration of NIV at the bedside which is best practice in all patients but essential in this population as patency of the upper airway should be ensured. Positioning of the patient to assist with maintenance of airway patency may be needed.

A common question that arises in the inpatient setting is when to commit a patient to long-term nocturnal NIV therapy on discharge after successful weaning from acute continuous NIV. Our approach is to first determine if chronic hypercapnia is likely to be present. If yes then nocturnal NIV may be indicated as long-term therapy for advanced COPD to reduce exacerbations, improve quality of life, and reduce mortality. There are no guidelines specifically for management of acute decompensated overlap syndrome. In fact, the ATS guidelines for Long Term Noninvasive Ventilation in Chronic Stable Hypercapnic COPD recommend screening for OSA before initiation of NIV specifically to identify patients with overlap syndrome who may require more nuanced approach to treatment. When able, we try to adhere to ATS guidelines and refer patients for close follow-up 2–4 weeks after exacerbation for further assessment of need for long-term CPAP vs NIV therapies [97].

4. Conclusion

In patients with COPD, the co-existence of OSA is associated with more pronounced hypoxemia and hypercapnia and worse clinical outcomes. Consequently, identifying who and how to treat these patients is of major importance. CPAP remains the gold standard of treatment and is recommended in all OSA patients with symptoms or systemic hypertension, although determining symptoms caused by OSA can be challenging in patients with COPD. Additionally, treatment should be considered in asymptomatic patients with moderate to severe OSA and COPD with pulmonary hypertension and comorbid cardiovascular and cerebrovascular disease, especially if significant hypoxic burden. CPAP is effective, but in patients with the overlap syndrome and daytime hypercapnia, high-intensity noninvasive ventilation aiming to lower $PaCO_2$ may have additional benefits. Additionally, in those with severe resting hypoxemia, supplemental oxygen improves survival and should be added to positive airway pressure. The role of alternative non-positive airway pressure therapies in the overlap syndrome needs further study.

5. Expert opinion

COPD is highly prevalent currently and estimated to increase markedly in the coming decades, particularly in women and in low-middle-income regions [98]. Although cigarette

smoking remains an important risk factor for COPD, there is increasing appreciation for the role of indoor and outdoor air pollution globally. Thus, physicians are likely to encounter more and more patients with COPD as well as with the overlap syndrome. The data in overlap syndrome are still evolving, but a number of points are offered regarding expert opinion and speculation regarding the years to come.

5.1. Importance of assessing sleep in patients with COPD

Some sleep assessment, be it objective or subjective, should be made in patients with COPD. The presence of obesity should lead to a more comprehensive sleep history and physical examination for OSA. The sleep history can help to identify factors that influence quality of life and could be therapeutic targets for some individuals. Objective testing with either home sleep testing or polysomnography may help to identify sleep apnea but also sleep hypoventilation syndrome. In addition, these data may be helpful prognostically in identifying patients at high risk of cardiometabolic sequelae. In the future, wearable technologies may be quite helpful in capturing night-to-night variability in COPD including response to therapy, encouraging adherence to treatment, and identifying exacerbations before they are clinically apparent [99].

5.2. Evolution of the field

Hypercapnic COPD patients benefit from noninvasive ventilation, and it is currently grossly under-utilized. Increased appreciation for the utility of NIV among non-sleep specialists, including pulmonologists, may help to improve the clinical outcomes of many patients. Other therapeutic advances in COPD and overlap syndrome have been rather modest emphasizing the under-utilization of positive pressure therapy in this context. Observational studies have strongly suggested improved outcomes with PAP therapy [100]. Disease variability in OSA and in COPD has been described, although minimal research has addressed endophenotypic variability in overlap syndrome per se. The data suggest that OSA endotypes are similar in COPD patients compared to non-COPD, although further studies are clearly required [101,102]. In theory, some subsets of overlap syndrome patients may be particularly high risk and/or highly amenable to a particular intervention. Personalized medicine approaches could be used to identify these subsets of patients in order to guide therapy accordingly. Multimodal biomarkers could be used for classification of patients to facilitate individualized care. Unsupervised clustering could also be used to identify subsets of patients that are not clinically obvious who may respond differentially to particular interventions. Only through ongoing basic, clinical, and translational research in this area is major progress likely to occur.

5.3. Key areas for further research

As with any exciting area, a number of avenues for future investigation are likely to occur within the next 5 years. We offer a few possibilities to prioritize subsequent research:

1. The BODE index is currently used quite commonly in COPD, although it fails to capture issues related to sleep apnea or sleep health. We propose in the future a modified BODE index which may provide a more comprehensive assessment of patients' well-being and overall mortality risk.

2. While advances in pharmacotherapy for COPD are rapidly occurring, many have not focused on the subset of patients with overlap syndrome. The new findings regarding dupilumab in COPD might suggest a particular role for biological interventions in overlap syndrome [103]. Bronchodilator studies of tiotropium and salmeterol have both shown improvements in nocturnal saturations without significant change in sleep quality, and the role of these interventions in syndrome is unclear [95,96].

3. The explosion of therapies for obesity has led to considerable discussion about the use of pharmacotherapy in patients with respiratory disease. Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) receptor agonists are both therapeutic targets pharmacologically which can be used to achieve weight loss in people with obesity [104,105]. Given the frequent occurrence of obesity in people with OSA and/or overlap syndrome, the use of these medications to improve cardiometabolic health deserves further study. Targeted prevention programs using diet and exercise could be used if high-risk patients could be identified a priori.

4. Multicenter randomized controlled trials will be needed to guide future therapy in overlap syndrome. We are aware of a number of ongoing mechanistic studies which will be required to design subsequent studies rigorously.

The ultimate goal of research in this field is to improve the quantity and quality of life for patients suffering with this morbid and common condition.

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Article highlights

- The overlap syndrome refers to the co-existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), and is associated with more pronounced sleep hypoxemia and hypercapnia and worse clinical outcomes than either COPD or OSA alone. Consequently, understanding who and how best to treat these patients is essential.
- Both COPD and OSA are heterogeneous disorders with a wide range of disease severities, and further research is needed to better characterize and prognosticate patients with the overlap syndrome to personalize treatment.
- CPAP remains the gold standard of treatment and is recommended in all OSA patients with symptoms or systemic hypertension, but sleep-related complaints are common in COPD and teasing out symptoms attributable to OSA in COPD can be challenging.
- Treatment should be considered in asymptomatic patients with moderate to severe OSA and COPD with pulmonary hypertension and comorbid cardiovascular and cerebrovascular disease, especially if significant hypoxic burden.
- CPAP is effective, but in patients with the overlap syndrome and daytime hypercapnia, high-intensity noninvasive ventilation aiming to lower $PaCO_2$ may have additional benefits.
- Supplemental oxygen should be added to positive airway pressure in patients with the overlap syndrome and severe resting hypoxemia.
- The role of alternative non-positive airway pressure therapies in the overlap syndrome needs further study.

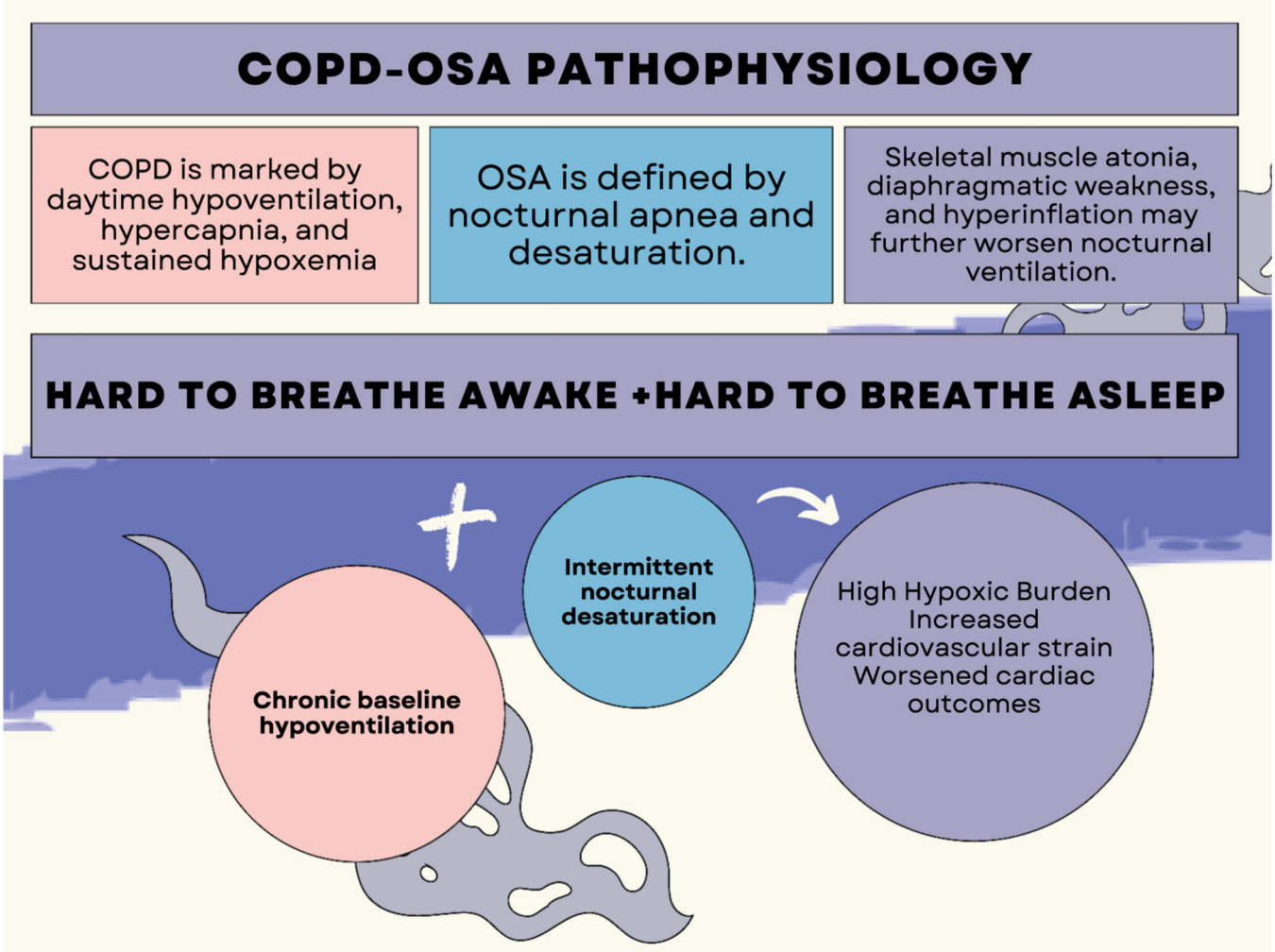

Figure 1.
Pathophysiology of overlap syndrome.

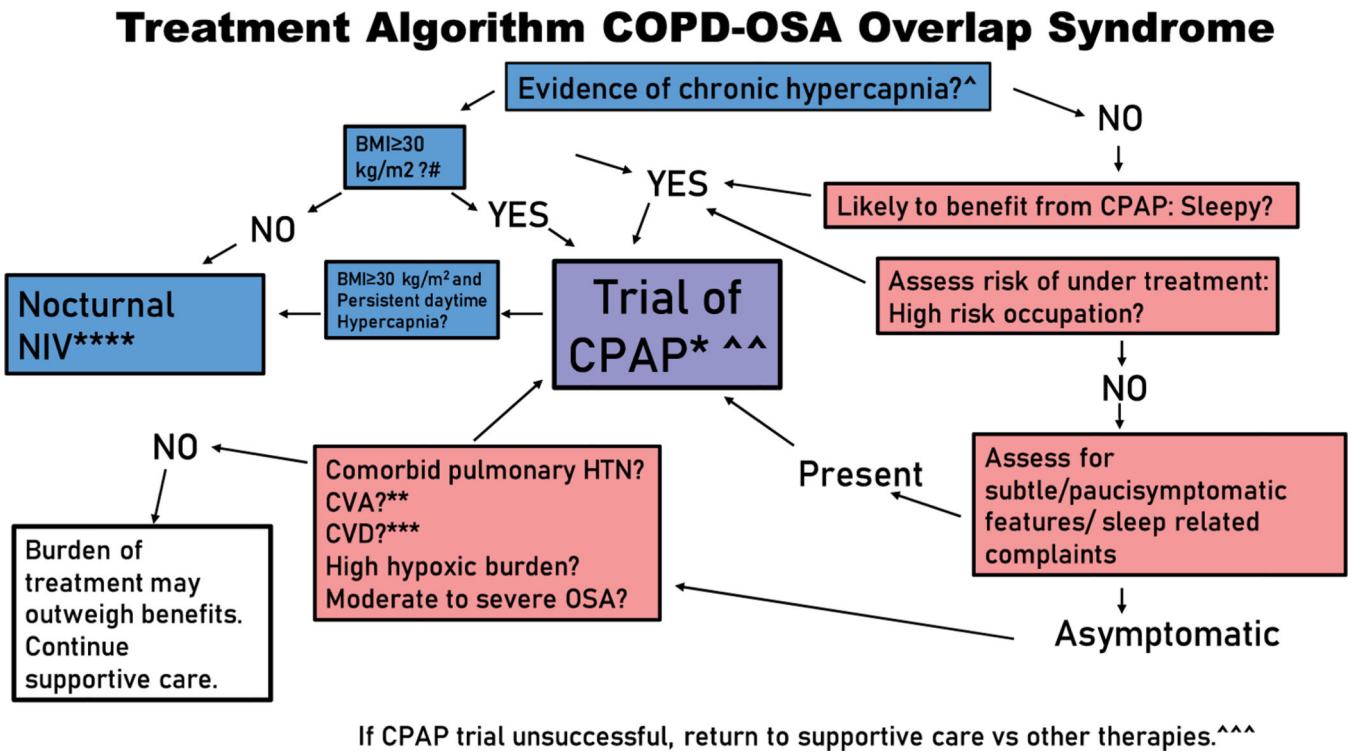

Figure 2.

Treatment algorithm COPD-OSA overlap syndrome.

*Continuous Positive Airway Pressure; **Cerebrovascular Accident; ***Cardiovascular Disease; ****Noninvasive Ventilation; #BMI ≥ 30 kg/m2 and hypoventilation may be consistent with obesity hypoventilation syndrome; ^Baseline PCO2 ≥ 45 mm Hg; ^^Trial of treatment is reasonable. CPAP preferred first line. Patient preference should be considered in regards to treatment modality. Risk benefits discussions with shared decision making should guide initiation of therapies; ^^^All patients should be counselled regarding risks of drowsy driving.

Table 1.

Who to treat with OSA in patients with co-existing pulmonary disease or the overlap syndrome (**bold**) and those without co-existing COPD.

OSA	Overlap Syndrome
• Sleepy	• Sleepy or **sleep-related complaints**
• Motor vehicle accidents, high-risk occupations	• Motor vehicle accidents, high-risk occupations
• Reduced sleep-related quality of life	• Reduced sleep-related quality of life
• Hypertension	• Hypertension
• Consider in patients with moderate to severe OSA and comorbid cardiovascular or cerebrovascular disease	• Consider in patients with moderate to severe OSA and co-morbid **pulmonary hypertension,** cardiovascular or cerebrovascular disease, **especially if high hypoxic burden**

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