

COPD-OSA OVERLAP SYNDROME EVOLVING EVIDENCE

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Objectives

- Look at the statistics of patients who suffer from overlap syndrome
- Describe exactly what is overlap syndrome
- Understanding the pathophysiology of overlap syndrome
- Describe the clinical consequences
- Describe various treatment options of overlap
- Reflect on some studies



Some Stats

- Chronic obstructive pulmonary disease or COPD is the 4th leading cause of morbidity and mortality in the United states
- The prevalence of this disease in adults is approximately 13.9%
- Obstructive Sleep Apnea is a disease impacting repetitive episodes of upper airway closure during sleep
- The prevalence of OSA is approximately 9% to 26% in adults
- The term “Overlap Syndrome” has been introduced to describe the association of both conditions in the single patient
- Currently it is believed that 10% to 30% have this “Overlap Syndrome”



So why is “Overlap Syndrome” such a big deal?

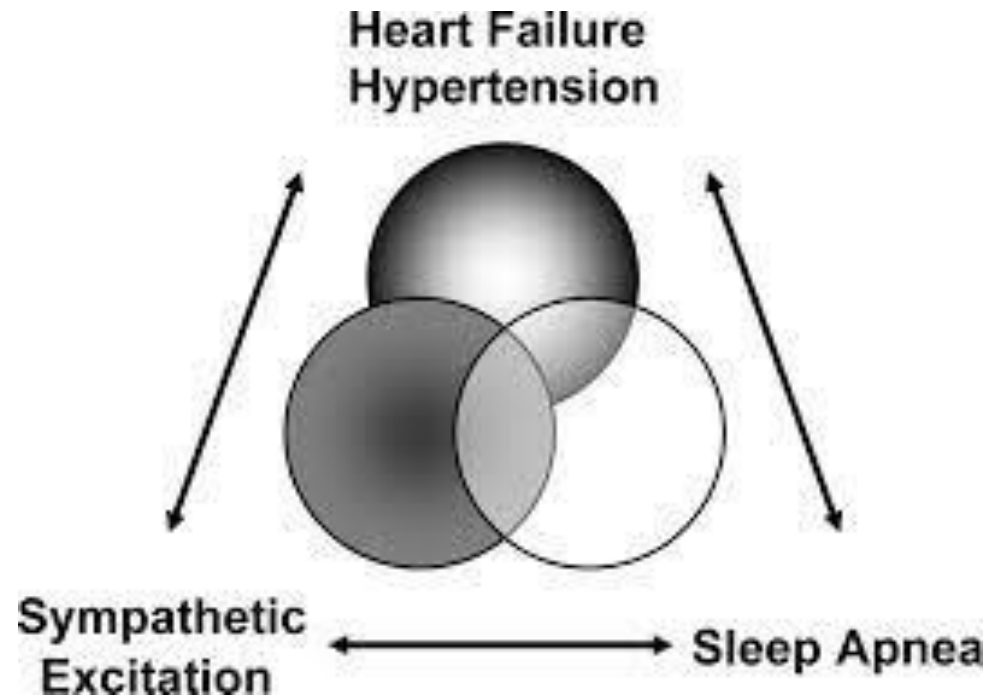
The precarious drop in oxygenation in patients with overlap syndrome put patients at significant risk for cardiovascular disorders

Patients with chronic obstructive pulmonary disease typically live at lower levels of oxygen as compared to the normal population and compared to patients typically with obstructive sleep apnea

Patients who suffer from overlap syndrome who are in REM sleep become severely hypoxic



So why is “Overlap Syndrome” such a big deal?



- When the brain senses low levels of oxygenation and wakes you up there's a surge of catecholamine release creating a sympathetic response
- This in turn releases three important hormones dopamine, norepinephrine, and epinephrine.
- Increased sympathetic nervous system activity has been implicated as a primary precursor of hypertension
- This leads to increased pulmonary arterial pressures and hypertension leading to right heart sided failure



What is COPD?

- It is estimated that there are approximately 250 million people in the world who have chronic obstructive pulmonary disease
- In the United States it is estimated that 16 million people suffer from chronic obstructive pulmonary disease
- Some of the risk factors involved with chronic obstructive pulmonary disease is smoking, air pollutants, early childhood infections, genetics, and occupational exposure
- Typical symptoms include shortness of breath that gradually gets worse overtime, coughing with or without sputum production , wheezing , tightness of the chest, and sometimes weight loss



What is COPD continued

- Chronic obstructive pulmonary disease can lead to difficult sleeping patterns
- Chronic obstructive pulmonary disease leads to damage to the small airway resulting in oxygen not being able to be transferred over into the capillary membrane for cellular uptake
- Chronic hypoxemia in COPD it's quite common resulting in patients needing supplemental oxygen in order to survive
- Patients with moderate to severe COPD have an oxygenation saturation of 88% to 92%
- Saturations of 88% or below require oxygen
- Saturations below 84% require the patient to go to hospital

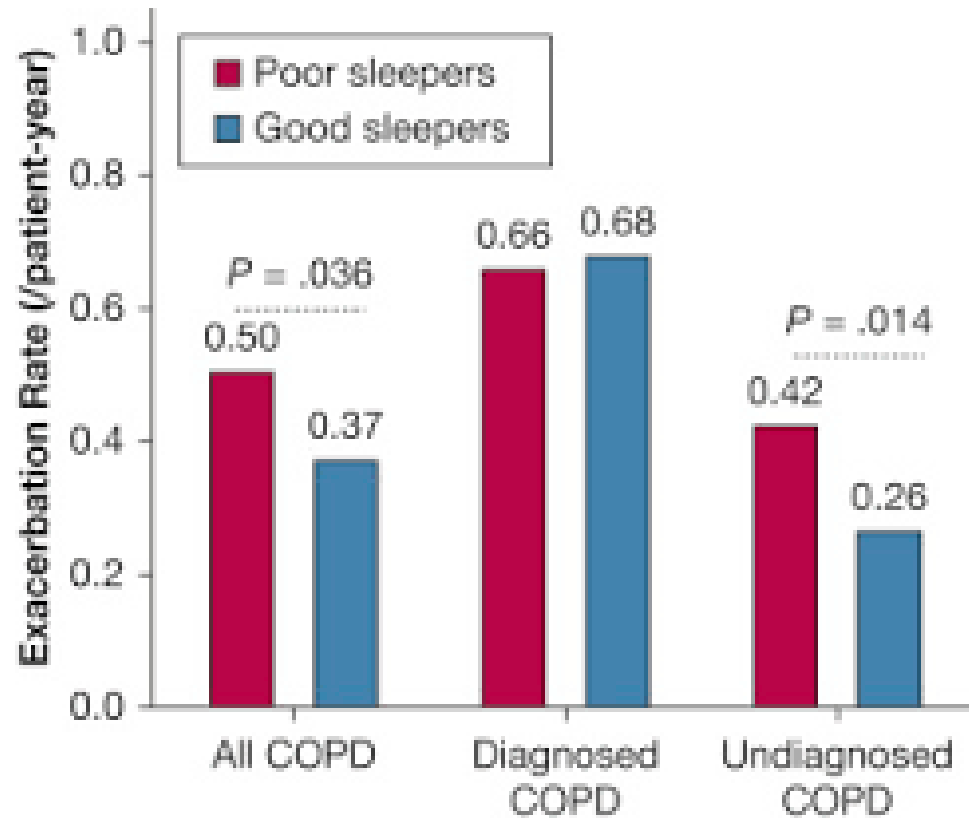


What is obstructive sleep apnea?

- It is estimated that globally about 20% of the world has some form of obstructive sleep apnea
- In the United States sleep apnea impacts about 30 million people but only 6 million have been diagnosed
- African Americans, Native Americans, and Hispanics
- Obstructive sleep apnea impacts men more than women
- Risk factors for obstructive sleep apnea are genetics ,being older, certain medications, lying on your back during sleep ,smoking ,and being obese
 - Notably antihistamines, benzodiazepines, barbiturates, and opiates
- When we sleep, upper airway muscles collapse over the airway even though there is a respiratory drive to breathe initiated by the diaphragm



Understanding sleep in COPD and OSA



- Patients with COPD often complain of poor sleep quality and fatigue during the day
- COPD patients frequently have nighttime arousals resulting in inadequate sleep
- 39% of patients with COPD complaining of nocturnal cough difficulty in maintaining sleep
- If a cough and wheeze are both present 53% of them have difficulty initiating and maintaining sleep
- Clinicians need to differentiate between isolated nocturnal hypoxemia and COPD versus hypoxemia due to obstructive airways hypoventilation in OSA



Differentiate between isolated nocturnal hypoxemia with COPD versus hypoxemia due to obstructive airways hypoventilation in OSA

Isolated hypoxemia is defined as the partial pressure of oxygen (PaO_2) less than 55 mmHg or oxygen saturation of less than 88% for at least five minutes during sleep

Sleep hypoventilation is defined as the increase in partial pressure of carbon dioxide (PaCO_2) more than 55 mmHg for 10 minutes during sleep

OR

Increase in PaCO_2 by 10mmHg above awake supine value over 50mmHg for 10 minutes



Understanding sleep in COPD and OSA

- Sleep disordered breathing in COPD patients is mainly seen in the REM phase of sleep due to reduced intercostal muscle activity and chest wall mobility
- This hypotonic muscle activity during sleep results in a severe drop in minute ventilation in COPD patients.
- It is estimated that the fall in minute ventilation from wakefulness to non-REM sleep is approximately 16% and the minute ventilation drops further to 32% in REM sleep
- This drop-in minute ventilation and the decrease in tidal volume result in more pronounced hypoxia and hypoventilation



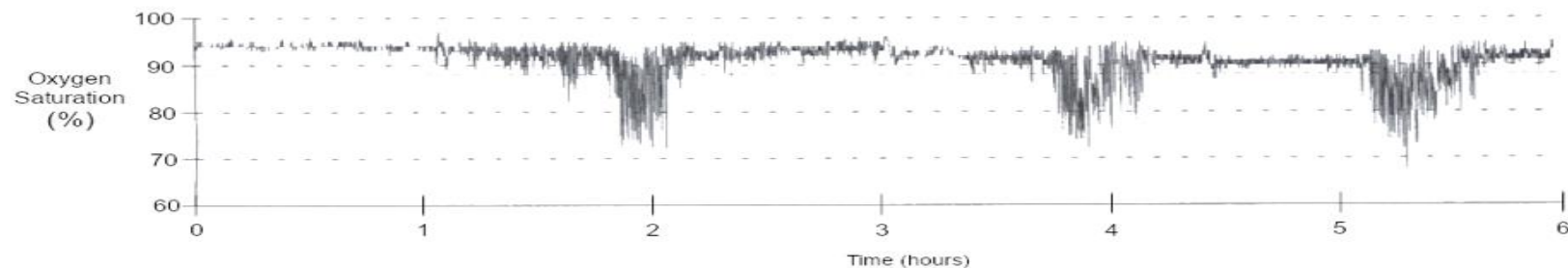
Understanding sleep in COPD and OSA

- Further reduced chest wall mobility and relaxation of intercostal muscles during REM phase precipitates nocturnal hypoxia and reduces the functional residual capacity (FRC) in these patients.
- This results in rapid shallow breathing pattern during the REM sleep which further reduces the alveolar ventilation



Nocturnal oxygen desaturation in COPD patients

- Nocturnal oxygen desaturation (NOD) is considered as the most common consequences of disturbed sleep in COPD
- Three mechanisms that contribute to NOD in COPD
 - Alveolar hypoventilation
 - Decreased ventilation-perfusion matching
 - Decreased end-expiratory volume (ERV)
- Patients with Overlap Syndrome have increased risk of NOD as compared to COPD patients resulting in respiratory failure and hypercapnia.



Hypoxia and systemic inflammatory mediators resulting in endothelial dysfunction

Underlying hypoxemia results in the release of inflammatory mediators including C-reactive protein, interleukin 6, nuclear factor Kappa beta, tumor necrosis factor , and interleukin 8

Intermittent hypoxia also induces oxidative stress with the release of reacting oxygen species mainly from the leukocytes

Ultimately resulting endothelial dysfunction and atherosclerosis



Risk factors smoking and obesity

- Cigarette smoking is a common risk factor for both COPD and OSA.
- Smoking promotes oxidative stress and release of inflammatory mediators thereby accelerating the underlying pathophysiologic process
- Obesity is considered is another risk factor for OSA
- Adipose tissues stimulates them to release inflammatory mediators such as tumor necrosis factor α and interleukin 6 predisposing to a pro-inflammatory state and oxidative stress
- Truncal obesity may reduce the chest wall compliance and respiratory muscle strength thereby resulting in ventilatory disturbances and ventilation-perfusion mismatching



Clinical consequences of Overlap Syndrome

- Increased risk of mortality due to cardiovascular events
- Hypoxic drive leads to oxidative stress
 - Release of systemic inflammatory mediators
 - TNF- α , IL-6, IL-8, and CRP
 - Endothelial dysfunction and atherosclerotic plaque formation
- OSA also results in metabolic dysfunction including insulin resistance and abnormal lipid metabolism
- OSA is also associated with systemic hypertension which increases the risk of coronary artery disease, congestive heart failure, arrhythmias and stroke



Clinical consequences of Overlap Syndrome

- Patients with Overlap Syndrome have increased risk of pulmonary hypertension and right heart failure secondary to underlying NOD, daytime hypoxemia and hypercapnia as compared to patients with COPD and OSA alone.
- Studies have shown that 86% of patients with overlap syndrome had pulmonary hypertension compared to 16% of the patients who have OSA alone
- Increased risk of developing pulmonary heart disease has also increased the frequency of deaths observed in sleep in OS syndrome



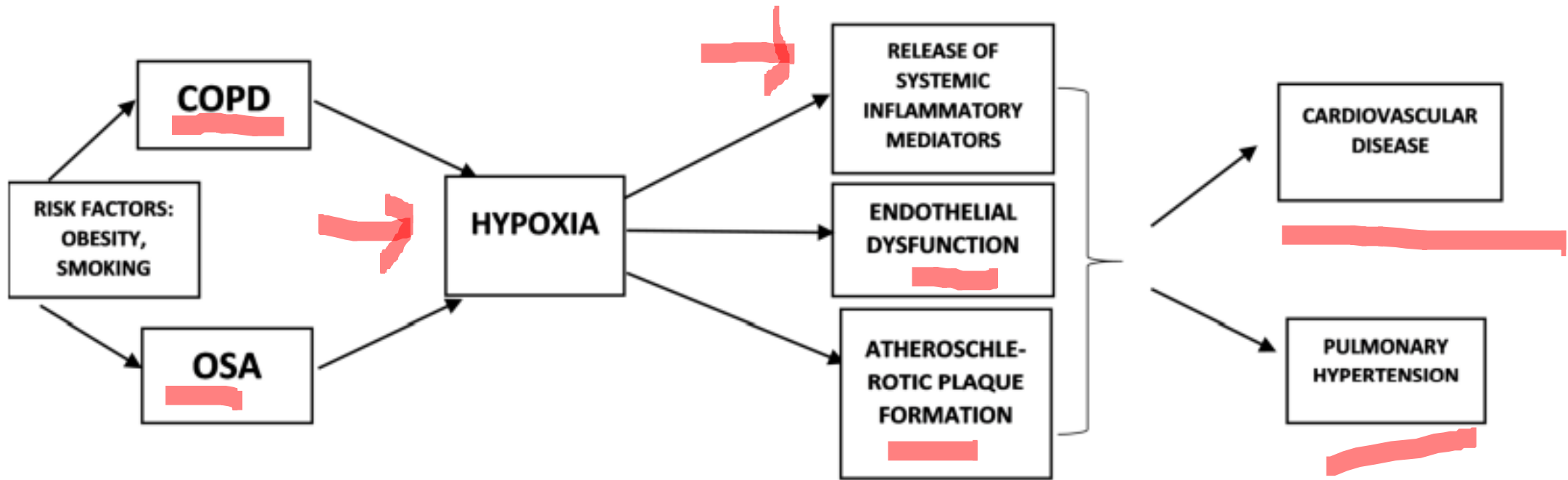


FIGURE 1: Summary of clinical consequences of overlap syndrome



The role of obstructive sleep apnea and oxygenation status

- Respiratory disturbances occurring during the nighttime in OSA patients were measured using Apnea Hypopnea Index, respiratory disturbance index (RDI), or SDB events
- CPAP was compared with O₂, CPAP was significantly more effective in reducing AHI
- Poor compliance
- While O₂ was shown to be more effective in elevating the mean SpO₂ during hypoxemic events (NOD- nocturnal oxygen desaturations)
- Overall, CPAP and nocturnal administration of oxygen both resulted in equivalent improvements in SpO₂, but only CPAP lowered the AHI, blood pressure parameters



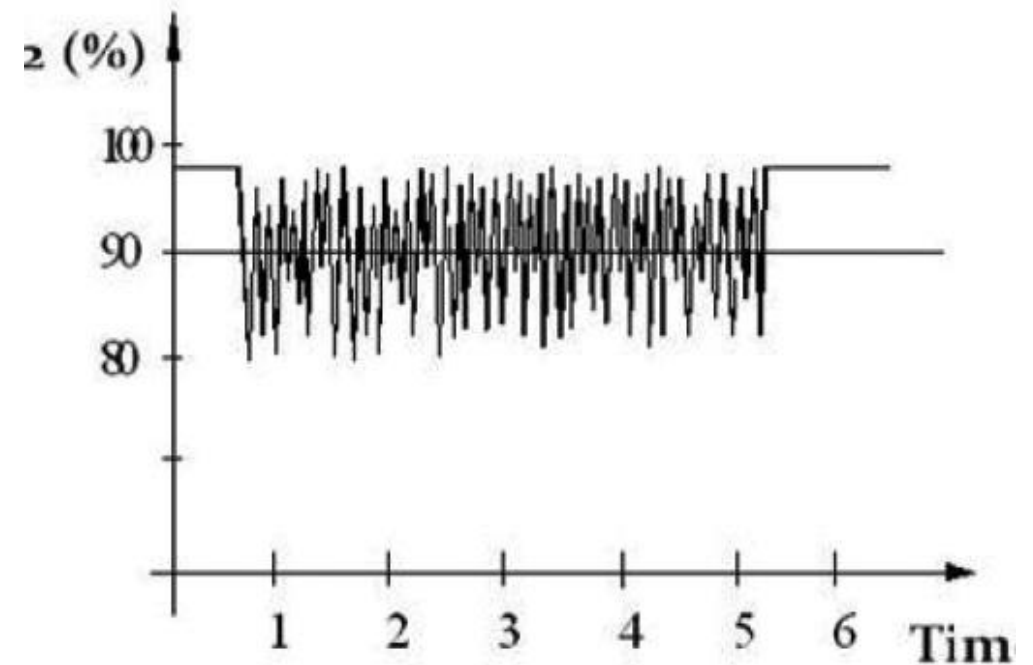
Clinical assessment of Overlap Syndrome

- Patients with COPD will generally report poor sleep quality and daytime fatigue
- OSA patients generally present with excessive snoring, unrefreshed sleep, and excessive daytime sleepiness.
- Polysomnography is the gold standard to detect sleep disorders in Overlap Syndrome
- Overnight oximetry can be used as a simple screening test to detect nocturnal hypoxia during sleep



Clinical assessment of Overlap Syndrome

- A cyclical (sawtooth) pattern on overnight oximetry may indicate sleep apnea in COPD patients and should be confirmed by polysomnography studies
- Gold Stages mild, moderate, severe, and very severe or 1-4
- The Sleep Heart Health study suggested that patients with mild COPD (GOLD stage I and II) may not reflect classic symptoms of OSA or may not have disturbed quality of sleep



Intermittent hypoxemia



Treatment Options

- Treatment of OSA in COPD patients can reduce cardiovascular mortality and improve the survival rate in these patients
- Treatment of OS should aim to maintain nocturnal oxygenation and reduce the episodes of hypoxemia and hypoventilation along with improving the sleep quality
 - Lifestyle Modifications
 - Supplemental Oxygen Therapy
 - Bronchodilators and Corticosteroids
 - Continuous Positive Airway Pressure (CPAP)
 - Non-invasive Ventilation (NIV)





Lifestyle Modifications

Structured exercise programs and pulmonary rehabilitation have been shown to be beneficial to patients with OSA and COPD

- Improvements to skeletal muscle wasting

- Improvements to daytime sleepiness

- Improvement in overall sleep quality have been demonstrated

- Significant reduction in AHI

- Increasing maximum oxygen consumption

Behavioral modifications it should be implemented

- Cessation of smoking

- Sleep hygiene techniques



Review Article | DOI: <https://doi.org/10.31579/2641-5194/020>

Role of Comprehensive Lifestyle Interventions in Managing Gastroesophageal Reflux Disease Complicating COPD-OSA Overlap Syndrome”

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Citation: Iqbal A. Khan, Hamza I. Malik (2021) Role of Comprehensive Lifestyle Interventions in Managing Gastroesophageal Reflux Disease Complicating COPD-OSA Overlap Syndrome J. Gastroenterology Pancreatology and Hepatobiliary Disorders 5(1) ; DOI: 10.31579/2641-5194/020

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Received: 26 February 2021 | **Accepted:** 09 March 2021 | **Published:** 20 March 2021



LIFESTYLE MODIFICATION RELATED TO GASTROESOPHAGEAL REFLUX DISEASE AND COPD OSA OVERLAP SYNDROME

- GERD is a prominent digestive disorder
- Patients with COPD have a higher risk of being diagnosed with GERD compared to those who don't have COPD
- Inhaled long-acting beta-agonists (LABA, anticholinergics and corticosteroids may decrease the lower esophageal sphincter (LES) pressure, facilitating reflux of gastric contents.
 - Treatment options
 - Avoid late night dinners
 - Keep head of bed elevated
 - Sleep in the left lateral position versus a right lateral decubitus position
 - Exercise





Supplemental Oxygen Therapy

Mainstay of management of COPD patients

Studies demonstrate that 18 hours of day of oxygen therapy can improve nocturnal hypoxemia and reduce the risk of mortality in these patients

Patients with overlap syndrome may be subjected to hypercapnia with the use of oxygen therapy.

Therefore, supplemental oxygen therapy is not typically recommended for overlap syndrome

Inappropriate long-term oxygen therapy in patients with borderline hypoxemia and OS may increase mortality, hospitalizations, and acute exacerbations

Exception

Supplementary oxygen therapy (with target SpO₂ of 88 – 92%) should be considered in patients with OS who continue to have hypoxemia despite PAP therapy



Pharmacological therapy

- Oxygen therapy improves nocturnal oxygen desaturation (NOD) with COPD patients
- Studies have shown that ipratropium bromide four times a day improves sleep quality and increases REM sleep in patients with moderate to severe COPD
- PAP therapy in overlap syndrome has been shown to reduce the need of bronchodilators with patients with COPD
- Both LABA (salmeterol) and LAMA (tiotropium) have been shown to increase nocturnal oxygen saturation without improving sleep quality



LAMA/LABA Combo Inhalers NEW INHALER ADDED

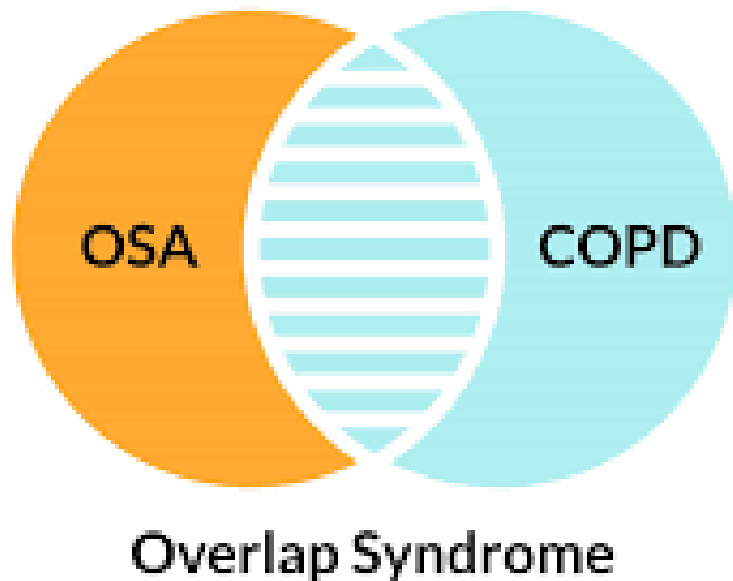
Brand	LAMA	LABA	Dosing
Anoro Ellipta	umeclidinium	vilanterol	1 puff daily
Bevespi Aerosphere	glycopyrronium	formoterol	2 puffs BID
Stiolto RespiMat	tiotropium	olodaterol	2 puffs daily
Duaklir Pressair	acbadinium	formoterol	1 puff BID



Pharmacological therapy

- 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.
- However, others have suggested that ICS may predispose to myopathy which may worsen upper airway collapsibility leading to OSA
- Sedatives and opioid should be avoided in COPD patients due to the risk of worsening central hypoventilation





The use of respiratory stimulants in overlap syndrome

- There are no studies examining the use of respiratory stimulants such as acetazolamide in Overlap syndrome .
- 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).
- Hence, respiratory stimulants are not currently recommended in overlap syndrome





Continuous Positive Airway Pressure (CPAP)

CPAP therapy is the most effective treatment for obstructive sleep apnea and overlap syndrome






Mechanism is the reduction of airway resistance and thereby reduces nocturnal hypoventilation

There is a marked reduction in reactive oxygen species related to obstructive sleep apnea and improvements of FEV₁, PAO₂, PACO₂, and mean arterial pressure

CPAP therapy can improve the survival outcomes of patients who suffer from COPD and obstructive sleep apnea and thereby reducing COPD exacerbations



Symptomatic response to CPAP in obstructive sleep apnea versus COPD- obstructive sleep apnea overlap syndrome: Insights from a large national registry

Dan Adler  , Sébastien Bailly , Paola Marina Soccà, Jean-Paul Janssens, Marc Sapène, Yves Grillet, Bruno Stach, Renaud Tamisier , Jean-Louis Pépin 

Published: August 12, 2021 • <https://doi.org/10.1371/journal.pone.0256230>

Article ⌵	Authors	Metrics	Comments	Media Coverage
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Abstract

Introduction

Methods

Results

Discussion

Conclusions

References

Abstract

Background

The symptomatic response to continuous positive airway pressure (CPAP) therapy in COPD-obstructive sleep apnea overlap syndrome (OVS) compared to OSA syndrome (OSA) alone has not been well studied so far. The aim of this study is to explore main differences in the clinical response to CPAP treatment in OVS compared to OSA alone.

Study design and methods



Symptomatic response to CPAP in obstructive sleep apnea versus COPD- obstructive sleep apnea overlap syndrome: Insights from a large national registry

- The aim of this study is to explore main differences in the clinical response to CPAP treatment in OVS compared to OSA alone.
- CPAP efficacy measured on the residual apnea-hypopnea index and adherence
- CPAP therapy was effective in normalizing the apnea-hypopnea index and significantly improved OSA-related symptoms, regardless of COPD status
- CPAP should be offered to patients with OVS on a trial basis as a significant improvement in OSA-related symptoms can be expected, although the range of response may be less dramatic than in OSA alone.



Non- invasive Ventilation (NIV)

- Noninvasive ventilation is effective in the management of COPD mainly with hypercapnic respiratory failure
- Noninvasive ventilation has been shown to improve nocturnal hypoxemia and quality of sleep with COPD patients alone
- Long term use of noninvasive ventilation in COPD patients helps improves lung compliance, prevents atelectasis, and reduces the work of breathing
- There is limited research and literature on the benefits of overlap syndrome and the use of noninvasive ventilation





Non-invasive ventilation (NIV) setup for COPD-OSA overlap syndrome: Is polysomnography (PSG) useful?

Maxime Patout, Gill Arbane, Jean-Francois Muir, Antoine Cuvelier, Nicholas Hart, Patrick Brian Murphy
European Respiratory Journal 2016 48: PA3063; DOI: 10.1183/13993003.congress-2016.PA3063

[Article](#)

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Abstract

Introduction: Current recommendation is to use PSG for setup of NIV in COPD-OSA.

Aim: To assess the clinical effectiveness at 3 month of a limited monitoring for NIV setup in COPD-OSA overlap compared of PSG.

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Safety and efficacy of auto-titrating noninvasive ventilation in COPD and obstructive sleep apnoea overlap syndrome

Patrick B. Murphy, Gill Arbane, Michelle Ramsay, Eui-Sik Suh, Swapna Mandal, Deepak Jayaram, Susannah Leaver, Michael I. Polkey, Nick Hart

European Respiratory Journal 2015 46: 548-551; DOI: 10.1183/09031936.00205714

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Auto-titrating NIV controls sleep disordered breathing and augments patient sleep comfort in COPD-OSA overlap <http://ow.ly/NtL24>

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RECENT
TRENDS
AND
FUTURE
DIRECTIONS

Studies on noninvasive
ventilation regarding
overlap syndrome

Studies comparing CPAP
versus noninvasive
ventilation



RECENT TRENDS AND FUTURE DIRECTIONS

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.

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.



Summary

- Overlap Syndrome Has been a significant impact on many patients who suffer from COPD and obstructive sleep apnea
- New research is being conducted on the best treatment options for these patients
- During evaluations of new patients, special emphasis must be placed on those who suffer from both disorders and see if there's an overlap component



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