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The overlaps of asthma or COPD with OSA: A focused review

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ABSTRACT

Asthma, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are the most common respiratory disorders worldwide. Given demographic and environmental changes, prevalence for each is likely to increase. Although exact numbers are not known, based on chance alone, many people will be affected by both lower airways obstruction and concomitant upper airway obstruction during sleep. Some recent studies suggest that there is a reciprocal interaction, with chronic lung disease predisposing to OSA, and OSA worsening control and outcomes from chronic lung disease. Thus, the combination of wake and sleep respiratory disorders can create an overlap syndrome with unique pathophysiological, diagnostic and therapeutic concerns. Although much work needs to be done, given the above, Respirologists, Sleep Medicine and Primary Care providers must be vigilant for overlap syndromes. Accurate diagnosis of, for example, OSA as a cause of nocturnal symptoms in a patient with asthma is likely to limit further ineffective titration of medications for asthma. Moreover, prompt treatment of OSA in the overlap syndromes will not only offer symptomatic benefit of OSA, but also improve symptoms and healthcare resource utilization attributable to obstructive lung disease, and in COPD, it may reduce mortality.

Key words: asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea, overlap syndrome.

Abbreviations: AASM, American Academy of Sleep Medicine; ACQ, Asthma Control Questionnaire; AHI, apnoea–hypopnoea index; CIH, chronic intermittent hypoxia; CPAP, continuous PAP; DTC, difficult-to-control; EDS, excessive daytime sleepiness; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; NIV, non-invasive ventilation; OSA, obstructive sleep apnoea; PAP, positive airway pressure; PEFR, peak expiratory flow rate; PSG, polysomnogram; QoL, quality of life; RDI, respiratory disturbance index; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; SHHS, Sleep Heart Health Study; SpO_2, oxygen saturation.

INTRODUCTION: BASIC DEFINITIONS AND EPIDEMIOLOGY

Asthma, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are the most prevalent chronic respiratory disorders worldwide.[1] Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow limitation; it affects up to 1–18% of the population in different countries.[2] COPD is characterized by persistent respiratory symptoms and non-reversible air-flow limitation that is usually progressive and most commonly arises from cigarette smoking and exposure to pollutants.[3] Roughly 10% of the world population over age 40 years has clinically important COPD, with the majority of patients remaining undiagnosed and untreated.[4] Both these obstructive lung diseases evolve on a background of local inflammation that is more recently recognized to be linked with systemic inflammation as well, and carry considerable morbidity and mortality. Interestingly, classical studies have shown increased nocturnal morbidity and mortality[5]; for example, in asthma, 68% of deaths occur between midnight and 08:00 h,[6] with similar findings for those admitted during exacerbations of COPD. It is also worth noting that although there is substantial heterogeneity among patients with asthma or COPD, in practice, most patients are treated according to guidelines rather than with individualized therapy.

OSA is defined by repeated episodes of upper airway occlusion that result in brief periods of breathing cessation (apnoea) or a marked reduction in flow (hypopnoea) during sleep, with subsequent repetitive inspiratory efforts against the occluded airway, arousal from sleep and oxyhaemoglobin desaturation—all of which have neurocognitive and cardiovascular sequela.[7] Excess

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weight is the most common risk factor for OSA, especially in Caucasians, although about one-third of patients are not overweight or obese.[8] Although prevalence estimates will vary based on the race, age and weight of the population studied, in the developed world, owing to population ageing and rising obesity rates, OSA has reached epidemic proportions. Thus, although the prevalence of symptomatic OSA (apnoea–hypopnoea index (AHI) >5 events/h) was close to 4% in 1993, by 2013 the estimated prevalence was 14% for men and 5% for women.[9] While this rise was demonstrated in the US, it is likely true throughout the developed world.[10]

David Flenley[11] was the first to coin the term 'overlap syndrome' referring the coexistence of COPD with OSA, although he acknowledged other lung diseases could overlap as well. He considered the overlap syndrome to have important clinical and therapeutic implications, different from the presentation and management of each underlying disorder. However, this somewhat imprecise definition—allowing for a mix of diseases (COPD phenotypes, cystic fibrosis and idiopathic pulmonary fibrosis) that have a spectrum of severity—did not focus on the possibility of interacting pathophysiological links, such that each disease might promote the development or aggravate the other, and at the time, asthma was not considered. This review focuses on the literature concerning the evolving concept of 'overlaps', specifically, with asthma and COPD.

EPIDEMIOLOGY: MERE COEXISTENCE OR AN INTERACTION?

As indicated above, these are common diseases. Thus, even by chance alone, either asthma or COPD will commonly coexist with OSA. There is considerable variability in the estimates of OSA prevalence in these diseases, owing to: (i) the method used to define OSA and (ii) the heterogeneity of the populations studied with regards to age, weight and smoke exposure. This makes it difficult to use prevalence studies alone to look for interacting pathophysiology whereby one disease predisposes or worsens the other. Moreover, shared conditions such as gastro-oesophageal reflux disease and obesity could worsen both the upper and lower airway diseases, which have further brought into question the existence of an apparent versus real overlap. Below, we review published data that suggest bidirectional pathophysiology.

Does asthma lead to OSA?

Epidemiological and observational studies suggest that asthma is a risk factor for OSA. Early questionnaire-based cross-sectional studies, such as the European Community Health Respiratory Survey, revealed a higher prevalence of self-reported habitual snoring and witnessed apnoea in patients with asthma, as compared with those without asthma (14.7% vs 9.2% and 3.8% vs 1.2%, respectively), and these associations remained when adjusted for BMI, age, gender and smoking status.[12] Similar associations have been seen in more recent cohorts from around the world.[13,14]

There are only few polysomnogram (PSG)-based studies that assessed OSA prevalence among patients with asthma, regardless of their sleep symptoms (see Table 1). Although these were relatively lean subjects, there was a higher than expected prevalence of OSA. Furthermore, no correlation was found between OSA severity and BMI or neck circumference,[15] suggesting a more unique pathophysiology of OSA among patients with asthma. Of note, in the study of Yigla *et al.*, 90–100% of subjects reported classic OSA symptoms such as snoring and EDS. Altogether, these studies lend support to higher rates of symptoms and OSA diagnosis in asthma compared with general populations.

Furthermore, a more recent report from a longitudinal study suggests asthma could have a pathogenic role in OSA, and that the upper and lower airways are indeed 'united'. In a 4-year prospective study of a population-based sample of 547 subjects free of OSA at baseline on two consecutive laboratory-based PSG studies conducted 4 years apart, patients with asthma had a 39% increase in the risk of developing incident OSA, as compared with controls, independent of the baseline covariates, including AHI, BMI and BMI change over time. Moreover, the risk for incident OSA with habitual sleepiness was 2.7 times higher in asthmatic individuals than those without asthma. This risk was dose-dependent on asthma duration: for each 5-year increment in asthma duration, the risk for incident OSA and for OSA with habitual sleepiness increased by 7% and 18%, respectively.[22]

COPD and OSA

Whether COPD predisposes to OSA is an open question, as this overlap illustrates particularly well the challenges of trying to determine the prevalence of such a disorder. A recent systemic review by Shawon *et al.* concluded that overlap syndrome was not common in the general population (prevalence: 1–3.6%), but was highly prevalent when populations of either COPD or OSA were assessed.[23] Among the COPD populations, prevalence estimates vary widely, depending on the population studied: from 0.5% in individuals with generally mild COPD (Sleep Heart Health Study, SHHS[17]) to 39% in those with moderate-to-severe COPD (in a US Veteran Population[20]) and up to 65% in those with the most severe COPD (a pulmonary rehabilitation population).[21] Although this would seem to suggest that there is a dose-dependent response that implicates COPD in the pathogenesis of OSA, there are several considerations to acknowledge. First, the prevalence of both COPD and OSA will be affected by age. Second, the severity of COPD may impact the measurement of OSA severity as assessed by the AHI. The definition of hypopnoea relies on oxygen desaturation. Patients with COPD with borderline hypoxaemia (who live on the steep part of the oxyhaemoglobin dissociation curve) will desaturate more quickly for a small degree of upper airway obstruction. Thus, for the same amount of upper airway collapsibility, there might be very different assessments of OSA severity depending on the underlying lung function. Indeed, the high prevalence of OSA in other lung diseases that can lead to hypoxaemia such as idiopathic pulmonary fibrosis appears to be driven by an increased number of hypopnoeas, not by an equal rise in both hypopnoeas and apnoeas (which are not defined by oxygen

Table 1 Studies reporting prevalence of sleep apnoea (diagnosed on objective testing) in patients with asthma and COPD

Study/design	Sample size	Main characteristics	Methods (type of sleep study/respiratory signal used for scoring/OSA definition	OSA prevalence	Other important findings	Comments
Asthma						
Yigla *et al.*,[15] prospective cohort followed over 8.9 ± 3.3 years	22	DTC asthma; 9 M/13 F; BMI 29.8 ± 1.1; age 49.3 ± 2.75; all on ICS, by DTC definition	Laboratory-based PSG/thermocouples, no nasal pressure/RDI ≥5/h	95.5%	(1) No relationships of RDI with neck size/BMI or their changes in time (2) Worse OSA severity in continuous oral corticosteroid users versus those who had received ≥2 bursts/year	Small *n*; respiratory scoring not detailed
Julien *et al.*,[16] prospective cross-sectional	26/Group	Severe/moderate asthma/controls matched for BMI (27.8/27.8/26.6) and age (48.8/47.9/45.5 years)	Home-based PSG/thermocouples and nasal pressure/scoring per Chicago criteria with hypopnoea defined by 4% desaturation and ±arousal/OSA defined by: (i) AHI > 15 (with arousal); (ii) AHI 4% and (iii) AHI 4% with EDS	AHI ≥ 15: 88/58/31% AHI 4% ≥ 5: 50/23/12% AHI 4% ≥ 5 + EDS: 42/15/4%	Among subjects with asthma, no significant correlations between the severity of sleep-disordered breathing with asthma severity or control measures (including ICS dose expressed in fluticasone equivalents)	Small *n*; all patients with asthma on moderate-high ICS dose
COPD						
Sanders *et al.*[17]	4670	Sleep Heart Health Study—drawn largely from cardiovascular cohorts, mean age 66.5 years (in subjects with obstruction on spirometry) and 62.2 years (no obstruction)	Unattended home PSG, thermistor based, hypopnoea defined by 4% desaturation 1132 participants had obstructive lung disease that was predominantly mild (FEV_1/FVC: 63.8%)	In those with no lung disease (FEV_1/FVC > 70%), 18.6% had AHI > 15/h In those with lung disease, 14.0% had AHI > 15/h Not statistically different	(1) An FEV_1/FVC value less than 65% is associated with increased risk of sleep desaturation (2) Desaturation is greater in patients with both lung disease and OSA compared with each of these alone (3) Individuals with generally mild OAD and without SAH in the community have minimally perturbed sleep	Few patients with more severe lung disease
Bednarek M *et al.*[18]	676	Community based; mean age 56.6 years	Both full PSG and respiratory monitoring. Used a 2% cut-off value to define hypopnoea	In those with no lung disease (FEV_1/FVC > 70%), 12.2% had RDI > 15/h In those with lung disease, 8.3% had RDI > 15/h Not statistically different	(1) In the OSA group, mean arterial blood saturation was lower and time spent on desaturation was longer than in OSA syndrome	Few patients with more severe lung disease

Table 1 Continued

Study/design	Sample size	Main characteristics	Methods (type of sleep study/respiratory signal used for scoring/OSA definition	OSA prevalence	Other important findings	Comments
López-Acevedo *et al.*[20]	73	Veterans administration retrospective cohort (age not reported)	Based on existing PFT and sleep study results	29/73 had overlap 23/79 had OSA alone	Daytime hypercapnia correlated with worse RDI ($P = 0.01$) and with worse nocturnal desaturation ($P = 0.01$)	Retrospective, small, VA population, referral bias
Soler *et al.*[21]	44	Cohort study of patients referred for pulmonary rehabilitation; mean age 68.1 years in COPD/OSA and 67 years in COPD/no OSA	At home polysomnography, with 3% desaturation rule	29/44 had OSA	Most severe group of COPD patients studied. Sleep quality also poor in this group	Small *n*

AHI, apnoea–hypopnoea index; DTC, difficult-to-control; EDS, excessive daytime sleepiness; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; OAD, obstructive airway disease; OSA, obstructive sleep apnoea; PFT, pulmonary function test; PSG, polysomnogram; RDI, respiratory disturbance index; SAH, Sleep apnea-hypopnea; VA, Veterans Administration.

desaturation).[24] Regardless, the pathophysiological consequences of intermittent desaturations in the cardiovascular system and brain are well established,[25] and those few known in the lung are discussed below.

The largest study—SHHS—has not shown an increased risk of OSA in COPD. This could be due to the fact that it enrolled subjects with generally mild airways obstruction, who entered the study at an older age (mean: 66 years), and were tested solely with the older thermistor technology.[17] Since OSA rates escalate most during 30–60 years of age and accelerates mortality,[26,27] it is possible that many, particularly those with more severe obstruction, would have died and could not be captured in this study. It is also possible that there may be no increased risk, and that the two diseases only coexist by chance; however, detection and treatment of OSA could still have important pathophysiological consequences, thus implications for management. For example, approximately 11% of patients with OSA have a moderate degree of airflow limitation on spirometry defined by a forced expiratory volume in 1 s (FEV_1) to forced vital capacity ratio of <70%.[28]

PATHOPHYSIOLOGY: WHAT FACTORS MIGHT CONTRIBUTE TO THE OVERLAP?

How these diseases interact is not known with certainty. However, we briefly review known mechanisms of interactions (Fig. 1).

Can asthma and/or COPD predispose to OSA?

Asthma and COPD alter upper airway anatomy and function

The Starling resistor is often used to model the upper airway in OSA.[29] This model has two variables which determine the flow through the upper airway: the critical closing pressures of the tissues (so-called Pcrit) and the resistance of the upstream segment—that is the nasal passages and tissue above the area of collapse. Both asthma and COPD, particularly with active smoking, are associated with chronic mucosal inflammation, and tonsillar and adenoid hypertrophy, which will

Figure 1 Possible pathophysiological links between chronic lung disease, and treatments for chronic lung disease, and obstructive sleep apnoea (OSA).

increase upstream resistance,[30] and perhaps collapsibility, favouring the development of OSA. Recent data have shown the ability of therapies targeting nasal inflammation (e.g. nasal corticosteroids and montelukast) to improve OSA.[31,32] Upper airway patency can worsen at night due to redistribution of dependent oedema in the supine position; this narrowing is worse in states of fluid overload such as cor-pulmonale.[33]

Asthma and COPD might also reduce upper airway muscle function, either directly via inflammation (neuropathy affecting sensory pathways) or indirectly via medication (corticosteroids) side effects that impact the ability of activated muscles to preserve airway patency. The effect of commonly used inhaled corticosteroid (ICS) on the upper airway anatomy and muscles is complex. Treatment for 4 months with high-dose inhaled fluticasone propionate not only increased wakefulness tongue strength but also decreased endurance,[34] in a pattern much like what has been reported in untreated OSA patients.[35] Although the overall collapsibility improved following fluticasone treatment, in the subset of patients who were older, men and with less well controlled asthma at baseline, the collapsibility increased. Furthermore, in a subset of subjects studied with magnetic resonance imaging, there was fat accumulation in the upper airway structures. The 4-month treatment represents a short window in the life of an asthmatic patient, who often continues these treatments life-long. While long-term treatment as well as impact on other relevant upper airway functions such as swallowing remains to be studied, these findings suggest that in an already susceptible upper airway, ICS treatment may ultimately tilt the balance in favour of collapse. Even more indirectly, sleep deprivation, which could be caused by uncontrolled asthma or COPD, has been hypothesized to lead to increased upper airway collapsibility by decreasing genioglossal activity.[36]

Lung volumes in asthma and COPD, and impact on the upper airway

One interesting observation in OSA pathogenesis has been the direct link between the upper and lower airways, so-called tracheal traction.[37] That is, increased lung volumes exert a mechanical force—so-called 'tracheal tug'—that stiffens the upper airway and prevents collapse.[38] Relative to healthy controls, subjects with nocturnal asthma who are hyperinflated during wake experience an augmented decline in functional residual capacity (FRC), to levels comparable to those of control subjects during rapid eye movement (REM) sleep, explaining in part their larger increase in lower airway resistance.[39] This sleep-related airway–parenchymal uncoupling[40] has been attributed to inflammation in the small airways and alveoli, and could potentially reduce the protective impact of tracheal tug in the presence of 'remodelled' upper and lower airways. That is, for the same lung volume, patients with asthma might experience less tracheal traction during sleep. In the case of COPD, it was not clear that lung parenchymal destruction from emphysema and reduced tissue elastance would exert the same pull on the large airways. However, Biselli *et al.*[41] measured upper airway collapsibility and found that patients with hyperinflation did have less upper airway collapsibility, and indeed, radiographical signs of hyperinflation were associated with reduced OSA severity.[42] These data would refute the hypothesis that tissue destruction causing hyperinflation in severe COPD would contribute to OSA pathogenesis.

Can OSA impact the lower airways?

In the presence of asthma or COPD, there is a complex cellular milieu that leads to the clinical features consisting of mucus secretion, bronchial reactivity and remodelling of airway walls and parenchyma. For each disease, a variety of cells, including eosinophils and neutrophils among others are involved, leading to disease heterogeneity. Several existing phenotypes and endotypes are being recognized.[43] Up to 60% of patients with asthma with persistent symptoms have a non-eosinophilic type of asthma.[44]

Interestingly, recent human and animal studies suggest that OSA could influence the lower airway inflammation and remodelling. In asthma, for instance, in a subset of 139 participants in the Severe Asthma Research Program (SARP) studied with induced sputum and other measures of inflammation, a higher risk for OSA was strongly associated with higher sputum neutrophils, more so after adjusting for other potential contributors such as obesity.[45] In 55 difficult-to-treat patients with asthma studied with respiratory polygraphy and bronchoscopy, the proportion of sputum neutrophils was higher in OSA than non-OSA patients, paralleled by higher levels of interleukin (IL)-8 and matrix metalloproteinase-9. Altogether, these two studies suggest that OSA shifts the airway inflammation of asthma towards a more non-eosinophilic, Th-1 phenotype, known to be poorly responsive to current standard therapies.[46]

Similarly, OSA can contribute to airway inflammation in adults with COPD as demonstrated by the increased levels of neutrophils, TNF-α and IL-8 in the bronchoalveolar lavage of adults with COPD and OSA as compared with adults with COPD only.[47]

Animal studies using chronic intermittent hypoxia (CIH)—a hallmark feature of OSA—extend these clinical observations. CIH altered the pattern of allergen-induced lower airway inflammation, protease/antiprotease balance, induced lung tissue remodelling including proximal airway wall fibrosis and 'emphysema-like' formations in the lung periphery which culminated in physiological deficits of expiratory flow limitation. The clinical implications of these observations are not clear, but suggest that CIH induced by OSA could lead to structural lung parenchymal changes and physiological deficits.

OVERLAP OF ASTHMA AND COPD WITH OSA: WHAT ARE THE CONSEQUENCES OF THE OVERLAP?

Asthma and OSA

Data from cross-sectional and experimental studies link OSA with worse clinical outcomes in patients with asthma, across the healthcare continuum. In the outpatient setting, in a large sample of 472 outpatients with asthma at routine clinic follow-up, OSA risk was

Table 2 Effects of CPAP treatment for OSA on asthma outcomes. Study details presented at first reference

Outcomes	Changes with CPAP	Study/design	Sample size	Main characteristics	CPAP treatment duration/adherence	Method for OSA diagnosis
Symptoms	Improved nighttime ± daytime	Chan *et al.*[57]/single centre, 2-week blocks control-CPAP-off CPAP	9 subjects	Severe asthma/apnoea index = 21.1/h, minimum SpO_2 = 87%	2 weeks/no objective adherence	PSG (apnoea indices reported)
		Guilleminault *et al.*[58]/ single centre, before and after design	10 subjects	Asthma with moderate-to-severe obstruction (FEV_1: 54% predicted)/RDI = 51/h, minimum SpO_2 = 71%	6–9 months/no objective adherence	PSG
		Ciftci *et al.*[59]/single centre, before and after design	16 subjects	Nocturnal asthma/ AHI = 44/h, minimum SpO_2 = 65%	2 months/no objective adherence	PSG
		Serrano-Pariente *et al.*[60] multicentre, before and after design	99 subjects	Intermittent: 11% Mild-persistent: 17% Moderate-persistent: 48% Severe persistent: 24%/RDI = 46.3/h	6 months/objective adherence recorded and non-compliant subjects were not excluded	PSG (30% of patients) or cardiorespiratory polygraphy (70% of patients)
Rescue bronchodilator use	Reduced use	Chan *et al.*[57] Serrano-Pariente *et al.*[60]				
Composite measures (Asthma Control Questionnaire)	Reduced scores and proportion of subjects with not well-controlled asthma scores	Serrano-Pariente *et al.*[60]				
Exacerbations	Reduced	Serrano-Pariente *et al.*[60]				
QoL (asthma specific)	Improved mini asthma QoL scores	Lafond *et al.*[61]/single centre, before and after design	20 subjects	Stable asthma of various control levels/AHI = 48/h	6 weeks/CPAP use 6.7 ± 0.9 h (subjects excluded if CPAP use <4 h/night)	
Physiology/PEFR	Improved AM and PM pre-/ post-bronchodilator PEFR that paralleled the treatment period and returned to pretreatment levels during the CPAP off period	Serrano-Pariente *et al.*[60] Chan *et al.*[57]				

Table 2 Continued

Outcomes	Changes with CPAP	Study/design	Sample size	Main characteristics	CPAP treatment duration/adherence	Method for OSA diagnosis
Airway reactivity	No improvement in MCT PC20	Lafond *et al.*[61]				
	Reduction in proportion of subjects with positive bronchodilator response	Serrano-Pariente *et al.*[60]				
Physiology/FEV_1	No changes	Ciftci *et al.*[59] Lafond *et al.*[61] Serrano-Pariente *et al.*[60]				

AHI, apnoea–hypopnoea index; AM, morning; CPAP, continuous positive airway pressure; FEV_1, forced expiratory volume in 1 s; MCT PC20, methacholine challenge; OSA, obstructive sleep apnoea; PEFR, peak expiratory flow rate; PM, afternoon; PSG, polysomnogram; QoL, quality of life; RDI, respiratory disturbance index; SpO_2, oxygen saturation.

assessed with the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) and asthma control with a validated instrument, the Asthma Control Questionnaire (ACQ) which encompasses symptoms, rescue bronchodilator use and lung function domains. A high OSA risk on SA-SDQ was associated, on average, with a 2.9 times higher odds for not well-controlled asthma on ACQ, independent of other potential contributors for poor asthma control, including obesity.[45] Contrary to earlier beliefs that OSA would relate most to nocturnal asthma symptoms, in a large sample of 752 asthma patients, an OSA diagnosis predicted a 2.1-fold higher odds for persistent daytime and 1.5 times higher likelihood for persistent nighttime asthma symptoms, suggesting carry-over effects of the nocturnal obstructive pharyngeal airway disorder on asthma, just like on daytime hypertension.[48] Moreover, a recent small study[49] found that OSA severity correlates with FEV_1 decline over time. Patients with asthma with PSG-diagnosed OSA experienced a greater decline in FEV_1 over 5 years of follow-up, in relationship to severity of AHI: 72.4 ± 61.7 mL/year in severe OSA (AHI > 30/h), 41.9 ± 45.3 mL/year in mild-to-moderate OSA ($5 < \text{AHI} \leq 30$) and 24.3 ± 27.5 mL/year in those without OSA (AHI ≤ 5). Positive airway pressure (PAP) treatment for severe OSA patients, over the 2-year follow-up, attenuated the accelerated pre-study FEV_1 decline.

A recent retrospective analysis of the largest publicly available US inpatient dataset extends observations of OSA adverse effects on asthma, to the inpatient setting; data from 179 789 adults with primary asthma hospitalizations were analysed for associations of OSA diagnosis, separately from obesity, with hospital length of stay, total hospital charges and need for invasive respiratory therapy. In comparison to no disease, OSA lengthened the hospital stay, increased the need for invasive respiratory therapy and hospital charges. Additionally, the burden of OSA on health resource utilization was higher than that imposed by obesity, and the two co-morbidities together had multiplicative adverse effects on all outcomes reported.[50]

COPD and OSA

As might be expected, several studies have shown that those with COPD and OSA have more profound nocturnal oxygen desaturations and sleep disturbances compared with either disease alone.[17] However, interest in overlap syndrome was considerably heightened by reports from observational studies that suggested increased mortality in overlap syndrome compared with COPD and OSA alone. Marin *et al.* found decreased survival among patients with overlap syndrome compared with either COPD or OSA alone.[51] The use of continuous PAP (CPAP) eliminated the difference between COPD-only and overlap patients. That overlap syndrome patients using CPAP have reduced mortality compared with overlap syndrome without CPAP has now also been reported in other cohorts[52,53] Further exploring the observed therapeutic benefit of CPAP, Stanchina *et al.*[53] found that greater time on CPAP was associated with reduced mortality in overlap syndrome patients. It is important to note that these

data are not randomized. Thus, whether PAP use prevents worse outcomes or is associated with other behaviours (e.g. adherence to statin therapy) that improve outcomes in this group of patients is not known. However, data are emerging that show deleterious cardiac changes worse in those with overlap compared with COPD alone,[54,55] and these changes are generally driven by the burden of hypoxaemia.

One other important way that OSA could modify COPD is via alterations in breathing control. Specifically, patients with overlap syndrome exhibit hypercapnia with less severe lower airway obstruction. Based on the work by Resta *et al.*,[56] those with COPD alone typically did not exhibit daytime hypercapnia unless the FEV_1 was <50% predicted. In contrast, those with COPD and OSA exhibited hypercapnia when FEV_1 was still >60% predicted.[56] Hypercapnia with relatively preserved lung function should prompt an evaluation for OSA.

THERAPEUTIC IMPLICATIONS OF OVERLAP: CAN TREATMENT OF ONE IMPROVE THE OTHER?

Can treatment of asthma/COPD improve OSA?

It is possible that treatment of upper airway symptoms in asthma might improve upper airway collapsibility. As mentioned above, high-dose ICS had variable effects on upper airway collapsibility that were dependent on baseline characteristics.[30] Also, treatment targeting nasal inflammation has been a successful strategy to improve OSA in children, and might be of benefit in those with mild disease.

In COPD, treatment of obstructive lung disease can improve hypoxaemia, which could reduce the number of hypopnoeas. Improved COPD/reduction in oral steroids might also improve sleep continuity. Both of these effects could then reduce the number of hypopnoeas. In theory, then, improved COPD care might improve metrics of OSA severity.

Can treatment of OSA improve asthma?

Several non-randomized/not controlled prospective studies have reported on effects of CPAP treatment for OSA of various durations on asthma outcomes (Table 2). All show improved asthma symptoms, and many have improvements in patient-centric outcomes, such as exacerbations and disease-specific quality of life. For instance, the most recent and largest multicentre study by Serrano-Pariente *et al.*[60] examined the impact of 6 months of CPAP in 99 asthma patients with moderate-to-severe OSA. They found significant but small improvements in asthma control scores. While small, the percentage of patients with uncontrolled asthma decreased from 41.4% at baseline to 17.2% ($P = 0.006$) at the end of the study, and this benefit started to emerge as soon as 3 months; furthermore, CPAP reduced the asthma attacks from 6 months prior to the study (35.4% to 17.2%, $P = 0.015$).

In regards to impact on physiological measures, reports have been more variable depending on the metric and population studied. As might be expected, the Serrano-Pariente *et al.*'s study suggests benefits to be greatest in patients with moderate-to-severe versus mild–intermittent asthma, those with severe OSA (RDI > 30/h) and those adherent to CPAP (≥4 h/night).

Can treatment of OSA improve COPD?

As discussed above, treatment of OSA in COPD is associated with reduced mortality in observational studies. There are no prospective interventional studies specifically addressing this question in the overlap syndrome patients. There are also emerging data that early recognition and treatment of OSA in COPD is associated with reduced healthcare utilization.[62] Konikkara *et al.*[62] screened all patients admitted for COPD exacerbation who had a BMI > 30 kg/m^2 for OSA. If they screened positive for OSA, an expedited study was arranged on discharge and then CPAP therapy initiated if indicated. In the subsequent 6 months, those patients diagnosed and adherent to PAP therapy had a subsequent reduction in healthcare utilization (emergency room visits and readmissions) compared with the 6 months prior

Table 3 Suggested future directions emerging from the available studies

Direction	
Asthma/COPD → OSA	
	OSA incidence in these populations and its relationship with lung disease phenotypes
	Natural history of the interaction starting early in life (for asthma, in birth cohorts)
	Role of ICS in upper airway patency during sleep and other relevant functions (swallowing)
	Other potential underlying mechanisms unique to these patients
	Appropriate new methods to screen/diagnose OSA in these patients
	OSA evaluation frequency and its determinants in these patients
OSA → worse asthma/COPD	
	Define effects of CPAP treatment for OSA in RCT
	Role of other OSA treatment modalities
	OSA role in treatment algorithms for asthma/COPD
	Should asthma and COPD be an indication for treatment in mild OSA?
	OSA contribution to asthma/COPD phenotypes/endotypes?
	Mechanisms of OSA impact on the lower airway inflammation/remodelling

CPAP, continuous positive airway pressure; ICS, inhaled corticosteroid; OSA, obstructive sleep apnoea; RCT, randomized controlled trial.

to intervention, in contrast to those who were diagnosed but non-adherent, who had the same rate of healthcare utilization before and after diagnosis.

What is the optimal treatment for patients with OSA and COPD?

There are no studies addressing this question specifically in overlap patients. Supplemental oxygen therapy has been a main stay of therapy in COPD patients with severe daytime hypoxaemia (resting oxygen saturation ≤ 88%), and is associated with improvements in survival.[63,64] Recently, the Long-term Oxygen Treatment Trial (LOTT) study did not find benefit for supplemental oxygen therapy in those with more moderate hypoxaemia (resting arterial oxygen saturation (SaO_2): 89–93%), who presumably desaturate even more at night.[65] Only a single study to date has looked at supplemental oxygen therapy specifically in overlap patients. Alford *et al*. administered 4 L/min of supplemental oxygen to 20 men with both OSA and COPD. While nocturnal oxygenation improved, the duration of obstructive events increased by 5.7 s, resulting in an end-apnoeic partial pressure of carbon dioxide PCO_2 increase of 9.5 mm Hg.[66] Thus, oxygen alone should not be used in the management of patients with overlap syndrome. In addition, COPD patients who develop morning headaches after treated with nocturnal supplemental oxygen should undergo prompt testing for concomitant OSA.[11,67] There is a long history of the use of non-invasive ventilation (NIV) in those with severe COPD and hypercarbic respiratory failure. The most recent such study suggested an improvement in mortality when targeting normalizing the daytime pCO_2 levels.[68] There are no studies of NIV specifically in overlap syndrome patients. Another interesting question in those with both COPD and OSA is whether hypercapnia is due to COPD alone or some combination of COPD and OSA, that is, might treatment of OSA with CPAP (and not NIV) reverse some of the hypoventilation as has been shown in obesity hypoventilation syndrome?[69] The choice of optimal initial treatment of hypercapnic overlap syndrome patients remains unknown. It is worth noting that the American Academy of Sleep Medicine (AASM) recommends that patients with significant lung disease, such as COPD, not to be considered as candidates for automatic CPAP titration.[70] However, the AASM guidelines acknowledged a lack of available studies, and preceded the study by Guerrero *et al*.[71] who showed that the automated CPAP titration in patients with overlap syndrome was as effective as in patients with OSA alone.

WHERE NEXT?

While the field of Sleep Medicine has been dominated by Respirologists, our knowledge on the overlaps of obstructive lung disease with OSA has lagged far behind other areas. Much work remains to understand the broad range of subjects with overlap syndrome and how they are similar or different. Consider that two very different patients - one with severe COPD and mild OSA and one with mild COPD and severe OSA - will both be labelled as overlap patients. Yet, as we present, new data are forthcoming suggesting intriguing reciprocal links between asthma and/or COPD with OSA and an interactive pathophysiology. For example, nasal disease in asthma and corticosteroid effects could promote OSA; OSA, in turn, particularly related to intermittent hypoxia, might detrimentally impact the lower airways, worsening outcomes and mortality. Importantly, failure to diagnose OSA but instead stepping-up standard asthma treatments would simply accelerate this vicious cycle. Conversely, treatment of OSA with PAP has the potential to improve control of lung disease, quality of life and perhaps mortality. While this body of literature clearly represents an important step ahead in this nascent field, many questions of critical importance remain (Table 3).

What can clinicians do in the meantime? First, these overlaps are frequently unrecognized. Patients with asthma/COPD may not report sleep symptoms,[72] or may attribute them to the primary lung disease. Standard screening questionnaires are also imperfect.[73] Oxygen desaturation observed during the night should not only be attributed to lower airway disease. Providers must be vigilant and periodically consider the diagnosis of OSA, particularly in patients with lung disease of longer duration and increased severity, who are using higher doses of ICS, or who have shared risk factors such as obesity, nasal disease and gastro-oesophageal reflux. Second, physicians should recognize that treatment of patients with OSA and asthma or COPD has the potential to improve important patient-focused outcomes and may reduce healthcare utilization.

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