



Editorial

Obstructive Sleep Apnea Syndrome and Chronic Obstructive Pulmonary Disease: Overlap or Syndrome[☆]

Apnea obstructiva del sueño y enfermedad pulmonar obstructiva crónica: *overlap* o síndrome

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For epidemiologists, COPD and obstructive sleep apnea (OSA) are entities that are defined by easily determined variables, FEV₁/FVC < 0.70 and apnea–hypopnea index (AHI) > 5, respectively. In the case of COPD, however, things are somewhat more complicated, because the patient will also have respiratory symptoms and risk factors (e.g., a history of smoking).^{1,2} OSA is a clinical entity defined by the presence of 5 or more apneas or hypopneas per hour of sleep, that is to say AHI ≥ 5. When the patient presents associated daytime symptoms, the syndrome is defined as obstructive sleep apnea–hypopnea syndrome (OSAHS) or OSA.³

It is relatively simple to establish the prevalence of both COPD and OSA with the use of clinical questionnaires on respiratory diseases and sleepiness, spirometry, and sleep polygraphy. This methodology has been used to determine that the prevalence of COPD in Spain is 10%,⁴ and that OSA occurs in 19% of men and 15% of women.⁵ However, in none of these studies were tests performed simultaneously to determine the prevalence of COPD/OSA overlap. This information is of interest, because almost half of the specialist respiratory medicine consultations in Spain are for COPD and OSA.⁶ The few clinical studies available do not suggest that COPD patients have a greater concomitant prevalence of OSA, or vice versa.⁷ In an Aristotelian syllogism, one could assume that if 10% of the adult population has COPD and OSA coexists in 10–20% of them, the prevalence of COPD/OSA overlap will affect between 1 and 2% of the population.

For the clinician, quantifying the problem takes second place to recognizing the coexistence of the two entities and knowing how to manage them on an individual basis. COPD is a highly heterogeneous disease in terms of clinical presentation and prognosis. It is common to encounter a patient with a history of smoking and

excess weight/obesity who consults due to dyspnea on exertion, symptoms of chronic bronchitis, nonrestorative sleep, and tendency to retain fluids. This phenotype is reminiscent of patients with late-stage disease historically described as “blue bloaters”.⁸ We now recognize that many of these patients have OSA and/or nocturnal hypoxemia. Along the lines of the asthma/COPD overlap (ACO) syndrome, can we consider this type of patient as an “COPD/OSA syndrome” carrier? Might this be a COPD phenotype? In our opinion, the evidence is still insufficient to characterize these patients as such. Firstly, the risk factors for developing OSA among COPD patients are the same as among non-COPD patients: obesity, cranio-facial malformations, fluid retention.⁹ These factors are modifiable, and this does not fit well with the “irreversible” character of the syndrome or phenotype concept. Furthermore, we do not know if a specific “genotype” exists that predisposes smokers to develop COPD with a COPD/OSA profile.

From the OSA point of view, we know that significant inflammation occurs in the upper airway that diminishes with specific treatment.¹⁰ Moreover, in COPD patients, the level of inflammation of the lower airways is increased in the presence of OSA.¹¹ Finally, in mice exposed to intermittent hypoxia (a principal feature of OSA), alveolar damage occurs as a result of excess inflammation and local oxidative stress.¹² All these factors may contribute to the pathogenesis of COPD. In contrast, COPD as such does not determine the development of OSA, unless indirectly. For example, active smokers have increased upper airway inflammation that would aggravate OSA. Conversely, in advanced stages of COPD, when the patient loses weight, the severity of any coexisting OSA may be alleviated.

During sleep, COPD and OSA show variable degrees of sustained or intermittent systemic hypoxia, respectively. Basal SaO₂ and the intensity of nocturnal hypoxemia have been recognized for years as primary factors in the development of pulmonary hypertension (PH) in COPD.¹³ This relationship has not yet been established in patients with OSA alone. In patients with combined COPD and OSA, nocturnal O₂ saturation is more intense during the apneic episodes and, indeed, concomitant PH occurs more commonly than in patients with COPD or OSA alone.¹⁴ In addition to hypoxia, excess

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oxidative stress and sympathetic activity occur during sleep in both entities. Both phenomena are considered to be intermediate mechanisms behind the increase in cardiovascular morbidity and mortality in patients with either COPD or OSA; however, no synergistic effect has been demonstrated in patients with COPD/OSA overlap.

Arguments against considering COPD/OSA overlap as a syndrome include the absence of specific clinical or biological biomarkers, and the observations that the natural history of each entity appears to be the same as when it occurs alone, and no common treatment been identified for all COPD/OSA patients. As things stand, the diagnoses of COPD and OSA must be suspected and confirmed according to current guidelines.^{1,3} It is of particular importance that patients with COPD and OSA be treated on an individualized basis, and we recommend that these patients undergo manual titration in a specialized center. The specific mode of positive air pressure (CPAP, BiPAP) and the need for supplemental O₂ must be established during respiratory polygraph.

In the near future, research in this area will have to focus on the prevalence of OSA and/or nocturnal hypoxemia in COPD patients, and the influence of any overlap on the natural history of the disease. This clarification must be followed by clinical trials to improve current treatments. In this regard, the Spanish CHAIN cohort of COPD patients includes a substudy evaluating the coexistence of OSA.¹⁵ This ongoing study will provide significant prognostic data on the COPD/OSA entity and will define future treatment lines.

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