



# The impact of long-term conventional treatment for overlap syndrome (obstructive sleep apnea and chronic obstructive pulmonary disease) on concurrent erectile dysfunction

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## KEYWORDS

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QoL

## Summary

**Purpose:** To assess the improvement of concurrent erectile dysfunction (ED) in men with overlap syndrome (obstructive sleep apnea and chronic obstructive pulmonary disease), treated with continuous positive airway pressure (CPAP) and bronchodilators.

**Material and methods:** We evaluated 48 men of a mean age of  $52.8 \pm 10$  years suffering from both obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), and concurrent ED. They were treated with conventional for pulmonary obstruction therapy (CPAP and bronchodilators) for 6 months and then their erectile function (EF) status was reassessed. ED was considered as improved, if ED intensity score increased for at least five points compared to that of baseline. The determinants for improvement of ED were also evaluated, as well as patient's personal degree of satisfaction with the treatment they received as far as the disorder was concerned.

**Results:** EF was improved in 12 patients (25%), but only two thirds of them were satisfied with the grade of improvement after treatment. ED improvement was related positively with age and apnea/hypopnea index and negatively with ED duration. ED intensity score, O<sub>2</sub> saturation at night and BMI were not significantly related to the outcome of EF improvement.

**Conclusions:** Conventional treatment for OSA and COPD, has a positive effect on concurrent ED on the minority of patients. This effect is possibly due to the

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improvement of respiration during sleep with CPAP and of oxygenation with bronchodilators continuously. Of the improved men, one third was not satisfied with the impact of this treatment modality on their EF. It is likely that specific for ED treatment is needed in these individuals.

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## Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by repetitive episodes of upper airway obstruction with consequent blood oxygen desaturation, sleep fragmentation and excessive daytime somnolence.<sup>1</sup> Diagnosis is based on an overnight polysomnographic examination, during which hypoxic episodes, hypercapnia, transient awakening and fragmented sleep are recorded.<sup>2</sup> It is associated with obesity, hypertension and cardiovascular disease. Although the etiologic association between OSA and sexual disorders is controversial, it has been reported that the impairment of sacral segment function in OSA patients leads to the development of male sexual dysfunction.<sup>3</sup> However, sexual problems are commonly found in patients with sleep disorders and vice versa.<sup>4,5</sup>

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder resulting in many extra-pulmonary consequences. There is evidence that COPD is associated with sexual dysfunction and especially erectile dysfunction (ED), and that chronic respiratory failure worsening results in further sexual insufficiency.<sup>6</sup> In a national survey among patient associations, the rate of sexual dysfunction was approximately 40% in patients with chronic respiratory disorders.<sup>7</sup> Overlap syndrome (OS), a term introduced by Flenley,<sup>8</sup> describes the association and simultaneous presence of OSA and COPD. The prevalence of OSA in the community is reportedly about 4% in adult males of the fourth and fifth decade, and that of COPD is 1% of the general population.<sup>9</sup> OS in recent studies has a prevalence of 11% amongst patients with OSA and 14% amongst patients with mild COPD. The combination of the two disorders enhances the effect of each of them on nocturnal hypoxemia and O<sub>2</sub> desaturation.<sup>10</sup>

ED, has been defined by the NIH as the inability to achieve and maintain an erection sufficient for sexual intercourse. Its association with OSA and COPD<sup>7,11</sup> raises interest about the natural history and treatment of ED in cases with OS. In this study, we assessed the impact of conventional treatment, namely continuous positive airway pressure (CPAP) and bronchodilators, on concurrent ED in men with OS.

## Material and methods

Between January 2003 and February 2005, 720 new patients were diagnosed with COPD, in the outpatient clinic of the Pneumology Department. Two hundred and thirty five of them had stage 2 and 3 COPD ( $FEV_1/FVC < 70\%$  and  $FEV_1 < 50\%$ ), diagnosed according to the criteria of the European Respiratory Society.<sup>12</sup> Forced spirometry was done using a Morgan Flexiflo RS23C Interface spirometer (P.K. Morgan, UK). Patients with daytime sleepiness were also evaluated by Epworth sleepiness scale (ESS) and when the score was  $> 10$ , they underwent a full-night polysomnography examination in the sleep laboratory. Of those 235 patients, a total of 74 suffered also from OSA (apnea/hypopnea index (AHI)  $> 5$ , snoring, sleep fragmentation and daytime somnolence). Digital PSG recordings Systems (Somnostar  $\alpha$  Series; Sensor-Medics, Inc; Yorba Linda, CA, USA) were used. The following variables monitored: electroencephalogram (EEG, two paracentral, two frontal, two occipital) submental electromyogram (EMG), right and left electroculogram (ROC, LOC). Oronasal airflow was recorded by thermistors mounted over the nose and mouth and respiratory efforts were recording by piezo-electric bands. Arterial oxygen saturation (SaO<sub>2</sub>) was measured continuously via a non-invasive infrared finger probe. Electrocardiography (ECG) was recorded continuously between the forearms. The surface EMGs of both anterior tibial muscles were also recorded. The data received from the polygraph was digitally encoded and stored on a removable optical-laser-disc. The stored data was immediately available for study and scoring. PSG were scored manually using standard criteria for sleep stages.<sup>13</sup> An apnea was defined as a cessation of airflow lasting at least 10s, accompanied by a dropped of SaO<sub>2</sub> by more than 2% below the immediately preceding baseline.<sup>14</sup> Hypopnea was defined as a decrease of the airflow by a drop of SaO<sub>2</sub> by more than 2% below the immediately preceding baseline. CPAP titration was manually performed in the sleep laboratory during a polysomnographic study. Optimal CPAP was considered the lowest level of pressure that eliminated almost all obstructive respiratory events, including flow limitation events, in all body positions and in all

sleep stages. All patients suffered from OSA received CPAP therapy. According to the guideline for the management of COPD:2004 Revision,<sup>15</sup> bronchodilators used were the anticholinergic tiotropium once daily, the beta-agonists salmeterol and formoterol twice daily, and occasionally the methylxanthine, theophylline. Of the 74 patients with OS, 60 suffered from concurrent ED which had been diagnosed clinically, during diagnostic work up for pulmonary obstruction, when the ED intensity score<sup>16</sup> was  $\leq 20$  (Appendix). Patients with hormonal deficiencies or penile deformities and patients who were receiving or had received any medication for ED during the last month were excluded from the study. Thus, of the 60 patients that fulfilled the criteria for inclusion in the present study (COPD+OSA+ED), 48 participated while 12 were excluded or did not show interest in participating, for various personal reasons. Enrollment process of patients assessed for COPD, OSA and ED is depicted in Fig. 1.

After a 6-month treatment, the status of their erectile function was reassessed by ED intensity score. ED was considered as improved, if ED score increased at least five points compared to that of baseline. The five points cut off point was selected because it generally designates an individual change in ED severity scale. This must not be

confused with the overall change in ED score that patients reported as a group. Patients were also asked to answer with 'yes' or 'no' if they were satisfied with the effect of therapy on their sexual function.

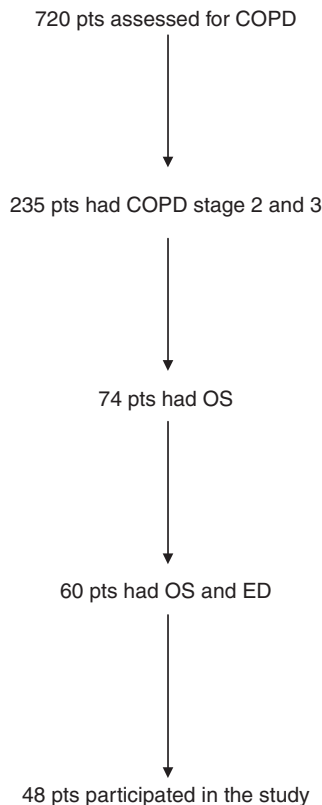
Primary outcomes were the difference in ED intensity score and the evaluation of the improvement of erectile function, as well as the satisfaction of the patients with treatment. Secondly, we evaluated the impact of age, body mass index (BMI), AHI, ED duration and nocturnal O<sub>2</sub> saturation on the improvement of the disorder.

After testing data for normality, statistical analysis was performed using the Wilcoxon signed ranks test, the Mann–Whitney test and  $\chi^2$  test. A forward stepwise logistic regression was used to assess the determinants for improvement of erectile function. Statistical significance was accepted at all times when  $P < 0.05$ . A commercially available statistical package was used to perform the analysis (SPSS 12.0 for Windows).

## Results

Mean  $\pm$  SD values of the studied men were for age  $52.8 \pm 10$  years, ED duration  $16.8 \pm 16$  months, AHI  $28.3 \pm 23.2$ , BMI  $33.8 \pm 4.3$ , O<sub>2</sub> saturation at night  $90.76 \pm 3.6\%$  and ED intensity score  $16.1 \pm 1.5$ . Demographics at baseline are shown in Table 1. All patients were overweight and heavy smokers, and had COPD of moderate severity.

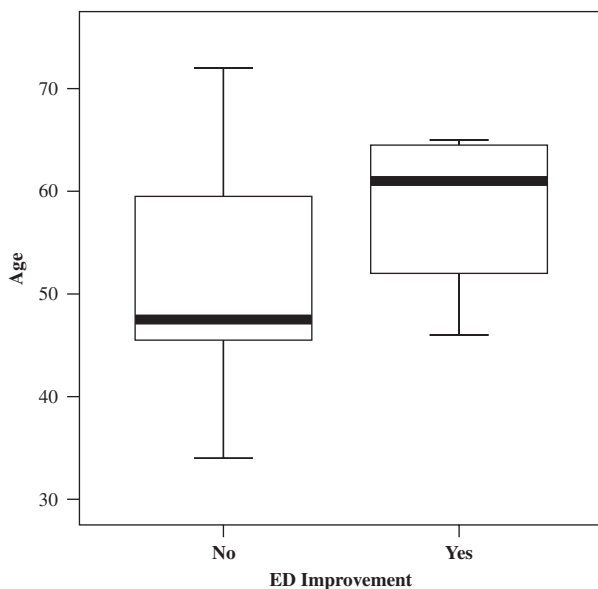
ED intensity score was improved in 12 (25%) of the studied patients, while the remaining 36 patients (75%) did not report an improved ED intensity score. Of the patients who experienced erectile function improvement, only 8 (16.6% of the studied population) were satisfied with their erectile function after treatment. Nevertheless, in the whole population of patients, improvement in ED was significant (Wilcoxon signed ranks test,  $P < 0.001$ ), but the patients, except of the above mentioned, were not satisfied with the effect of the treatment they received on their erectile function ( $\chi^2 P < 0.001$ ). Erectile function improvement was related positively with age and AHI and negatively with ED duration, while ED score, O<sub>2</sub> saturation at night and BMI had a small and non-significant relation to the outcome of ED improvement. Stepwise multiple regression analysis produced a model predicting ED improvement that included age, AHI and ED duration, although a model with ED duration alone was not predictive of the outcome of the treatment (Hosmer–Lemeshow statistic  $\chi^2 = 12.191$ ,  $P = 0.007$ ). The Hosmer–Lemeshow statistic indicated a good fit for the model



**Figure 1** Enrollment process of patients assessed for COPD, OSA and ED.

**Table 1** Demographics at baseline, for all patients and for the two groups of EF improvement outcome (mean  $\pm$  sd).

|                                  | Improvement      | No improvement   | All patients    |
|----------------------------------|------------------|------------------|-----------------|
| Age (years)                      | 58.25 $\pm$ 7.9  | 51 $\pm$ 10.1    | 52.8 $\pm$ 10   |
| Body mass index                  | 34.85 $\pm$ 3.4  | 33.4 $\pm$ 4.5   | 33.8 $\pm$ 4.3  |
| Apnea hypopnea index             | 44.9 $\pm$ 29.9  | 22.7 $\pm$ 17.8  | 28.3 $\pm$ 23.2 |
| Sat O <sub>2</sub> % (nocturnal) | 89.35 $\pm$ 5.4  | 91.2 $\pm$ 2.7   | 90.76 $\pm$ 3.6 |
| ED duration (months)             | 18.75 $\pm$ 13.7 | 16.17 $\pm$ 16.8 | 16.8 $\pm$ 16   |
| ED intensity score               | 14.8 $\pm$ 1.6   | 16.5 $\pm$ 1.2   | 16.1 $\pm$ 1.5  |

**Figure 2** Age of the two groups of patients regarding ED improvement ( $P = 0.031$ ).

( $\chi^2 = 9.08$ ,  $P = 0.247$ ). The model was able to correctly predict 94.4% of the patients who would not improve and 58.3% of the patients who would, for an overall success rate of 85.4%. Employing a 0.05 criterion of statistical significance, age, AHI and ED duration had significant partial effects. The odds ratio for age indicated that when holding all other variables constant, 1 year increase in age gave a 1.34-fold increase in the odds for improving, one point higher AHI increased by 1.08 the odds for improving while 1 month longer ED duration decreased the odds for improving (OR = 0.88).

In bivariate analysis, the patients that improved were older ( $P = 0.031$ , Fig. 2), had a higher AHI ( $P = 0.006$ , Fig. 3), a lower ED intensity score before treatment ( $P = 0.002$ ) and a higher score after treatment ( $P < 0.001$ ) than the others. The BMI ( $P = 0.315$ ), O<sub>2</sub> Saturation ( $P = 0.782$ ) and ED duration ( $P = 0.221$ ) before treatment did not differ significantly between the two groups.

## Discussion

OSA could be described as the intermittent failure to transport the full complement of nasal nitric oxide (NO) to the lung with each breath.<sup>17</sup> Thus, the dearth of NO has been implicated for the development of the OSA consequences.<sup>18,19</sup> The long-term complications of OSA, namely hypertension, atherosclerosis and coronary artery disease, which are in parallel associated with ED itself,<sup>20</sup> may be due to the repeated temporary dearth of NO in the tissues, secondary to a lack of oxygen, one of NO's two essential substrates.<sup>17</sup> The impairment of NO's vasoprotective function due to the respiratory disturbances during nighttime sleep might explain an etiologic association between OSA and ED. A number of clinical trials have shown the therapeutic impact of CPAP on the treatment of OSA. In an earlier study of 15 men with mild OSA treated for 12 weeks with CPAP, we reported a 24% success rate in sexual attempts.<sup>21</sup> Li et al.<sup>22</sup> treated 15 men for 1 month and reported a significant improvement in erectile function. Margel et al.<sup>23</sup> administered CPAP for at least 1 year to 60 patients with OSA and ED, and showed that 20% of men improved. In their study, the main predictor of erectile improvement was OSA severity.

COPD is characterized by partially reversible chronic airflow limitation, secondary to an abnormal inflammatory reaction in both airways and lung parenchyma. It is associated with several other systemic non-pulmonary consequences that add to the burden of disease and contribute significantly to a marked decrease in quality of life (QoL). Although the structural changes in airways and alveoli remodel the lung, COPD should be viewed by clinicians as a treatable condition, since most patients with COPD have an additional reversible component related to increased bronchomotor tone.<sup>24</sup> ED should be considered as a consequence of pulmonary obstruction which deserves to be treated. Long-term oxygen therapy has been studied for the reversal of sexual disorders in males

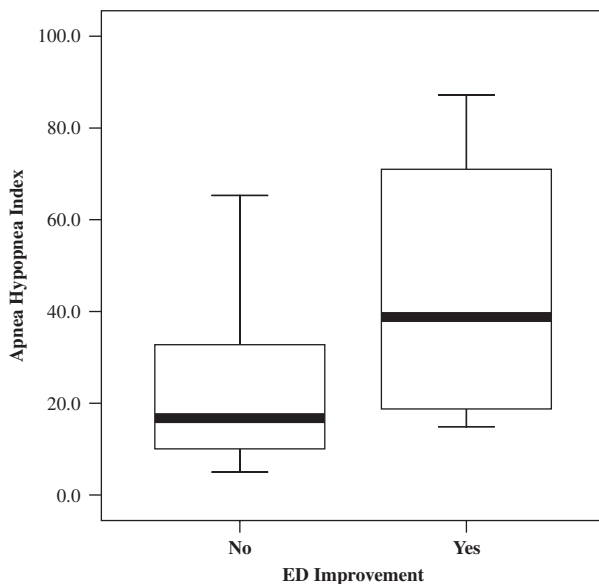
with COPD. Aasebo et al.<sup>25</sup> administered oxygen for one month and treated successfully impotence in 5 out of 12 patients. The responders showed a significant increase in arterial pO<sub>2</sub> and serum testosterone, and a decline in sex hormone binding globulin. Very short oxygen treatment did not improve impotence, despite a significant increase in pO<sub>2</sub>. Walbroehl<sup>26</sup> has reported that the medications used to alleviate COPD can both help and hinder sexual functioning. However, the relevant literature is poor as data reporting on any positive effect of conventional treatment for COPD on ED, besides oxygen, do not exist.

As a primary observation, the results of the present study suggest that the long term therapy with bronchodilators and CPAP of a specific group of men with OS and concurrent ED may improve the latter in about 25% of the cases. Interestingly, the improvement of ED in patients with OSA treated with CPAP has been reported between 20% and 33%,<sup>21,23</sup> approximately similar with the above mentioned. It must be postulated, that this improvement may be due to the improvement of oxygenation during sleep with CPAP and of respiratory function with bronchodilators continuously. One of the mechanisms proposed to be responsible for the ED in patients with OSA and/or COPD is endothelial dysfunction with overproduction of endothelin<sup>27,28</sup> and impaired NO availability in the peripheral blood.<sup>29,30</sup> Several studies have shown that continuous treatment with CPAP increases the levels of NO in OSA patients.<sup>29,31</sup> Additionally, the administration of bronchodilators improves expiratory airflow by reducing airway muscle tone. Tiotropium, a newer anticholinergic agent, dissociates slowly from M<sub>3</sub> receptors (34.7-h half-life) resulting in a high and constant 24-h bronchodilator activity.<sup>32</sup> Beta-agonists salmeterol and formoterol, compared to placebo, have both demonstrated greater FEV<sub>1</sub>, an index of airway caliber response, and peak expiratory flow improvement.<sup>33</sup> Theophylline, a nonselective phosphodiesterase (PDE) inhibitor, increases cyclic adenosine monophosphate and thus, relaxes the bronchomotor tone and produces systemic and pulmonary vascular dilatation. However, the successful targeting of PDE5 in the treatment of ED, irrespectively of the underlying pathology, with sildenafil and the newer PDE5 inhibitors, vardenafil and tadalafil, provides rational concept for the targeting of PDE in COPD treatment. The positive results from recent clinical trials examining the efficacy of selective PDE<sub>4</sub> inhibitors, cilomilast and roflumilast, offer some optimism.<sup>34</sup> Because of their class, it will be interesting to assess the impact of these agents on concurrent ED.

ED improvement was positively influenced by patient age and AHI, and negatively by ED duration. The fact that older patients are more likely to improve erectile function with treatment for OS may be due to lower expectations that older men have from their sexual life, so they easily capitalize any improvement of their sexual function. AHI was also found to be a determinant for improvement in a relative study of long term treatment with CPAP for patients with OSA and ED,<sup>23</sup> underlining the common clinical observation that the more severe pulmonary obstruction the higher improvement of concurrent ED. A longer duration of ED may reduce the residual erectile capacity in these individuals explaining the negative predictive role of this parameter. This must be taken into consideration by physicians in order to diagnose as early as possible ED in men with OS and manage it accordingly. However, the pathway of ED in OS, the mechanism of erectile function improvement with conventional treatment and the therapeutic impact of combinations of bronchodilators must be studied further in larger series of patients.

Sexual changes in males with chronic respiratory failure affect significantly not only patient QoL but also the quality of the relationship and the level of communication in the couple.<sup>6</sup> Improvement of subsequent sexual dysfunction must be one of the secondary goals of therapy as a health-related QoL (HRQoL) issue. The mean ED intensity score of the whole studied population was significantly higher after treatment compared to baseline, but the majority was not satisfied with erectile function status, as only one fourth of them crossed the five points improvement cut off change. Furthermore, one third of patients among those who had a higher than five points improvement were not satisfied with treatment impact on their sexual function. It is concluded therefore, that the observed improvement in ED score was not projected as a clinical improvement, either because of higher expectations or because of a still low score after treatment. Obviously, the status of sexual health and the relative satisfaction are influenced by satisfaction with treatment for the underlying pathology and relief of symptoms, and compliance with treatment. Thus, conclusions for satisfaction with treatment must be expressed cautiously unless well-designed studies assessing these particular parameters will be carried out. However, the advent of sildenafil, followed by the newer PDE5 inhibitors, revolutionarily changed the therapeutic management of ED. These agents, irrespectively of risk factors and comorbidities, influence local regulatory mechanisms and enhance erection by potentiating the smooth muscle-relaxing effects of





**Figure 3** AHI of the two groups of patients regarding ED improvement ( $P = 0.006$ ).

NO on resistance vessels and trabecular smooth musculature of corpus cavernosum. The experience with the use of sildenafil in the treatment of ED associated with OSA, which was superior in efficacy and satisfaction with treatment compared to CPAP,<sup>21</sup> suggests that specific for ED treatment may be needed in these individuals as well. Co-administration of CPAP, bronchodilators and PDE5 inhibitors would be also of utmost importance to assess improvement of sexual function and HRQoL in men with OS.

## Appendix. Erectile dysfunction intensity score

### Items

1. How often were you able to get an erection during sexual activity?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. When you attempted intercourse, how often were you able to penetrate your partner?
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

### Answers

For items 1 to 4 the possible answers are: Almost never or never; a few times (much less than half

the time); sometimes (about half the time); most times (much more than half the time); almost always or always, and are scored with 1, 2, 3, 4 and 5, respectively.

For item 5 the possible answers are: Extremely difficult; very difficult; difficult; slightly difficult; not difficult, and are scored with 1, 2, 3, 4 and 5 respectively.

### Total score

Add the scores for items 1–5 (possible maximum: 25).

### ED severity

Severe: 5–10; moderate: 11–15; mild: 16–20; normal: 21–25.

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