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·*Clinical Experience*·

# Sildenafil versus continuous positive airway pressure for erectile dysfunction in men with obstructive sleep apnea: a comparative study of their efficacy and safety and the patient's satisfaction with treatment

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**Abstract**

**Aim:** To assess the efficacy of sildenafil and continuous positive airway pressure (CPAP) in the treatment of concurrent erectile dysfunction (ED) with obstructive sleep apnea (OSA), and to gauge the level of treatment satisfaction in patients and their partners. **Methods:** Forty men were treated for 12 weeks with sildenafil 100 mg (20 men) or CPAP during nighttime sleep (20 men). Treatment efficacy was assessed by the rate of successful intercourse attempts, and satisfaction with treatment was assessed by patients' and partners' answers to question 1 of the Erectile Dysfunction Inventory of Treatment Satisfaction. **Results:** Under sildenafil, 128 of 249 (51.4%) intercourse attempts were successful; under CPAP, 51 of 193 (26.9%) attempts were successful ($^cP < 0.001$). Erectile function was improved in both groups. After sildenafil and CPAP treatment, the mean International Index for Erectile Function domain scores were 14.3 and 10.8, respectively ($^bP = 0.025$), compared to 7.8 and 7 at baseline, respectively. CPAP and sildenafil were well tolerated. Sporadic episodes of nasal dryness under CPAP and transient headache and flushing under sildenafil were not significant. Fifty percent of patients treated with sildenafil and 25% with CPAP were satisfied with the treatment, and their partners were equally satisfied. The satisfaction scores for both patients and partners under sildenafil were superior to those under CPAP ($^cP < 0.002$). **Conclusion:** Both sildenafil 100 mg and CPAP, used separately, had positive therapeutic impact but sildenafil was superior. Patients and their partners were more satisfied with sildenafil for the treatment of ED. However, because of the high proportion of dissatisfied men and partners, new therapeutic agents or a combination of the two methods must be studied further. *(Asian J Androl 2007 Mar; 9: 259–264)*

**Keywords:** obstructive sleep apnea; erectile dysfunction; continuous positive airway pressure; sildenafil

## 1 Introduction

Sleep apnea is a common disorder which causes a cessation or reduction of breathing during sleep, with consequent blood oxygen desaturation and sleep fragmentation. The disease affects almost every system of the body and

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results in daytime somnolence and neurocognitive defects [1]. Among its sequelae, erectile dysfunction (ED) has been reported as an early sign of nerve involvement. Fanfulla *et al*. [2] suggested that the impairment of sacral segment function in obstructive sleep apnea (OSA) patients is related to the development of signs of ED. However, Margel *et al*. [3] showed that only severe OSA is clearly associated with ED, and suggested morning tiredness and respiratory disturbance index (RDI) as predictive factors. Although the etiologic association between OSA and ED remains controversial, sexual problems are common among men with sleep disorders. Guilleminault *et al*. [4] reported an incidence of 48% of sexual problems among men aged 25–65 years with sleep apnea. Supporting these findings, studies of nocturnal penile tumescence in men with ED revealed a high rate of sleep disorders ranging from 44% to 61% [5, 6].

A dearth of nitric oxide (NO) has been implicated for the development of the OSA consequences [7]. NO deficiency and obstructive apnea are reportedly inseparable conditions [8]. ED, as a result of endothelial dysfunction, is often related with diabetes mellitus, atherosclerosis, hypertension and coronary artery disease; almost all are long-term complications of OSA. Logically, the association between OSA and ED might be explained by the impairment of NO vasoprotective function due to the respiratory disturbances during nighttime sleep.

Nasal continuous positive airway pressure (CPAP) is the treatment of choice for OSA and its sequelae [9]. Its efficacy has also been studied in the treatment of associated ED [10, 11]. The advent of sildenafil citrate, a PDE 5 inhibitor, revolutionized the treatment of ED [12, 13]. The initial results of its effectiveness in men with ED and OSA were promising [11]. In the present study we assessed and compared the efficacy of CPAP and sildenafil in the treatment of ED in men with OSA, and also assessed patients' and their partners' satisfaction with the treatment.

## 2 Patients and methods

The trial was prospective and randomized. It included 40 naive, consecutive cases of men with OSA who were found to suffer from concurrent ED. The sources of these patients were the outpatient clinic for sleep disorders and the laboratory for the study of ED of the Departments of Pneumonology and Urology of the University Hospital of Patras. At the sleep laboratory, they were evaluated for two consecutive nights for the purposes of diagnosis and one additional night for the therapeutic titration. Surface electrodes were applied to obtain an electroencephalogram (C3–C4, A1–A2, O3–O4), an electrooculogram, a mental electromyogram and an electrocardiogram. Expiratory airflow was detected by a nasal catheter. Any movements of the chest and abdomen wall were also examined. All of these variables were recorded on a polysomnograph that was synchronized to a data acquisition system (Somnostar A Series, SensorMedics, Bilthoven, The Netherlands). A fiberoptic oximeter to the polysomnography study system was used to measure the arterial oxygen saturation. Sleep stages and events were scored manually according to standard criteria. Apnea was defined as the complete cessation of airflow for at least 10 s and hypopnea as the reduction in airflow by at least 50% for 10 s or more. The number of apnea and hypopnea episodes per hour of sleep was measured by the RDI. An index of at least six respiratory events (apneas and hypopneas) per hour of sleep was required for the diagnosis of OSA and inclusion in this study.

Patients were asked to answer questions 3 and 4 of the International Index of Erectile Function (IIEF) questionnaire (see Appendix I). When the score was 4 or less for both questions they were referred for andrologic evaluation if they agreed. Within a 4-week baseline period a detailed history was taken, the men were physically examined, underwent laboratory, biochemical and hormonal tests, and completed an IIEF questionnaire form. Men who initially complained of ED, except for the standard andrologic evaluation mentioned above, were asked for sleep disturbances, somnolence and snoring, and referred to the sleep laboratory for monitoring when appropriate.

Patients were excluded from the study if they had a deformity of their external genitals, if they took nitrates, if they were already being treated for ED, if they had any hormonal deficiency, or if they had not been in a stable relationship for at least 6 months. Men who agreed to be treated signed a consent form and were randomly allocated, by a computer generation table of random numbers, to receive sildenafil 100 mg orally on demand, approximately 1 h prior to intercourse (20 men) or to be treated with CPAP in therapeutic levels at home during nighttime sleep (20 men) without taking any medication for ED. The duration of treatment was 12 weeks. The nature of the diseases and the details and goals of the

treatment were thoroughly explained to the couples. They were encouraged to attempt sexual intercourse and were instructed on manual stimulation during foreplay. They were also asked to report immediately after intercourse on the success of the attempt in a standardized event-log (Sexual Encounter Profile). Men were thoroughly instructed on how to take the medication or use the device and they were ordered to immediately refer any adverse effect. They were regularly assessed every 4 weeks and finally evaluated in detail at the end of the treatment period, when they completed an IIEF form and replied to the first question of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS, patient and partner version) [14]. The patient and his partner were considered "satisfied with the treatment" if the answer scored 4 or 5 (see Appendix II). Patients continued to receive medications regularly for their concomitant diseases throughout the study.

The primary outcomes of the study were the percentage of successful intercourse attempts and the satisfaction levels of the patients and partners with the treatment for ED. The secondary outcomes were the changes in IIEF domain scores and related adverse events. Statistical analysis was performed using paired[a] and unpaired[b] *t*-test, and the Mann–Whitney nonparametrical test[c]. Statistical significance was set to $P < 0.05$.

## 3 Results

### *3.1 Patients' profile*

In both groups, patients were matched for age, severity of OSA and ED duration. The baseline characteristics are shown in Table 1. They were also matched for IIEF domain score before treatment (mean score: 7 for CPAP-treated and 7.8 for sildenafil-treated). Comorbidities such as diabetes mellitus, atherosclerosis, hyperlipidemia, coronary artery disease and hypertension were evenly distributed in both groups. In general, 15 of 20 CPAP-treated patients and 14 of 20 sildenafil-treated patients suffered one or more concomitant diseases. All patients included in this study were heavy smokers, at least until recently, and all were also considered overweight.

### *3.2 Treatment efficacy*

Under CPAP, the 20 patients attempted intercourse for 193 times, with a mean of 9.65 attempts per patient during the treatment period. Of these attempts, 51 (26.9%) were successful. Under oral sildenafil the 20 patients attempted intercourse for 249 times, with a mean of 12.45 attempts per patient. Of these attempts, 128 (51.4%) were successful (Figure 1). Patients under sildenafil made more attempts than patients under CPAP (mean: 12.5 *vs*. 9.6; [c]$P = 0.002$), and were more successful (mean: 6.4 and 2.5; [c]$P < 0.001$).

IIEF domain scores were increased in both groups

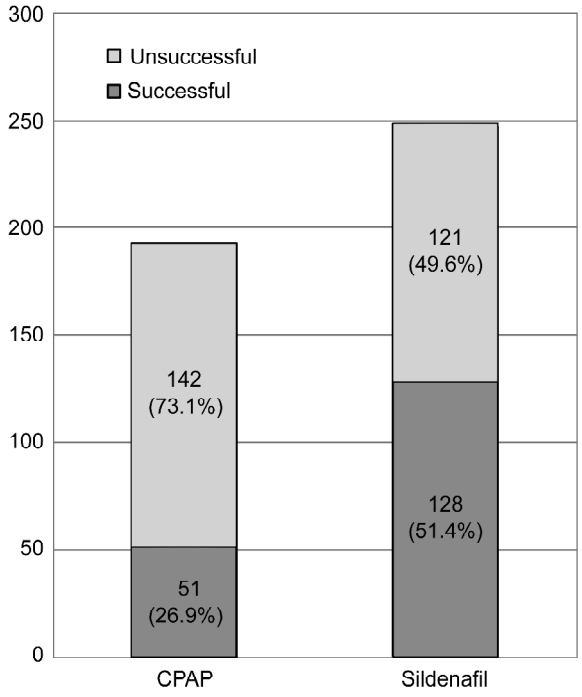


Figure 1. Overall number of attempts (successful and unsuccessful) for intercourse in patients treated for erectile dysfunction (ED) with continuous positive airway pressure (CPAP) and sildenafil.

Table 1. Characteristics at baseline of men with obstructive sleep apnea (OSA) and erectile dysfunction (ED) treated with continuous positive air pressure (CPAP) and sildenafil (mean values, range). *n*, number of patients; RDI, respiratory disturbance index.

| Treatment | *n* | Age (years) | ED duration (months) | RDI |
|---|---|---|---|---|
| CPAP | 20 | 55.5 (48–62) | 18.7 (8–36) | 8.9 (6–25) |
| Sildenafil | 20 | 55.3 (42–64) | 17.5 (6–36) | 9.9 (6–24) |

Table 2. International Index for Erectile Function domain score changes (mean ± SD) in patients treated for erectile dysfunction with continuous positive airway pressure (CPAP) and sildenafil. * $^{b}P = 0.025$, unpaired *t*-test; $^{a}P$, paired *t*-test. EF, erectile function; *n*, number of patients.

| Treatment mode | *n* | EF before treatment | EF after treatment* | $^{a}P$ value |
|---|---|---|---|---|
| CPAP | 20 | 7.0 ± 1.9 | 10.8 ± 4.4 | 0.002 |
| Sildenafil | 20 | 7.8 ± 1.2 | 14.3 ± 5.0 | < 0.001 |

Table 3. Erectile Dysfunction Inventory of Treatment Satisfaction Question 1 scores (mean, standard deviation). * $^{c}P = 0.007$; ** $^{c}P = 0.002$, Mann–Whitney nonparametrical test; *n*, number of patients.

| Treatment | *n* | Patient opinion* | Partner opinion** |
|---|---|---|---|
| CPAP | 20 | 2.4 ± 1.6 | 2.0 ± 1.4 |
| Sildenafil | 20 | 3.7 ± 1.4 | 3.3 ± 1.4 |

compared to baseline. In patients under sildenafil, the EF scores after treatment were higher than before (mean: 14.3 *vs.* 7.8; $^{a}P < 0.001$). In patients under CPAP the EF scores after treatment were also significantly higher than before (mean: 10.8 and 7.0; $^{a}P = 0.002$). However, after treatment, the group treated with sildenafil showed a significantly higher mean score of EF than the group of CPAP (mean: 14.3 *vs.* 10.8; $^{b}P = 0.025$; Table 2).

*3.3 Satisfaction with treatment*

Overall, 5 of 20 men (25%) were satisfied with CPAP for the treatment of ED but 10 of 20 men (50%) were satisfied with sildenafil. Satisfaction with treatment was significantly higher among the patients under sildenafil than that in the CPAP group ($^{c}P = 0.007$). The corresponding partners' satisfaction rates were 20% with CPAP and 50% with sildenafil. Satisfaction with treatment was significantly higher among the partners of the patients treated with sildenafil than that in the other group ($^{c}P = 0.002$). After the analytical assessment of answers given by the men and their partners, it was concluded that partners evaluate satisfaction with treatment differently, but not significantly, from the patients themselves. However, the satisfaction of patients and partners with sildenafil was clearly superior to that with CPAP. Scores of EDITS question 1 are shown in detail in Table 3.

*3.4 Safety*

CPAP and sildenafil were well tolerated. Nasal dryness was reported by four patients under CPAP treatment, and some episodes common for PDE 5 inhibitors, such as transient flushing and mild headache, were reported by three men treated with sildenafil. No adverse events were significant and no patient required any specific treatment, nor did they withdraw from the study.

## 4 Discussion

OSA-related complications, including ED, may be caused by the coordination of hypoxic episodes, which are common in sleep apnea, with arousal-related, end-apneic hyperadrenergic reactions [2]. This mechanism results in a key event: the reduction in circulating NO levels which increases platelet aggregation and vasoconstriction and impairs function of the vascular endothelial cells [15]. Because smooth muscle relaxation is brought about by the release of NO from the endothelial cells and the nerves supplying the erectile tissue, disturbances in this basic neurovascular event may cause ED.

It has been reported that CPAP treatment significantly improves subjective and objective sleep parameters in patients with OSA, and that men with more severe apnea may benefit more [16]. Consequently, several studies reported on the efficacy of this therapeutic method in the treatment of OSA-associated ED. Oxygen therapy for one month resulted in the reversal of ED in men with obstructive pulmonary disease [17]. CPAP provided either in the short term or for 12 weeks improved erectile function in men with OSA and ED [10, 11]. CPAP also had a positive impact on ED in the long term (12 weeks); predictors of erectile improvement were the severity of OSA (high RDI and low minimum oxygen saturation of hemoglobin during sleep) and the compliance with CPAP [18]. The effectiveness of CPAP may be due to the increase of NO circulating levels and the consequent improvement of endothelial cell function [15]. Interestingly, Margel and co-workers [18] reported on a subset of patients in whom erectile function deteriorated following CPAP. However, one of the main characteristics of that subset was non-compliance to CPAP. The treating phy-

sician should be aware of the proper use of the device and of treatment compliance when assessing CPAP effectiveness.

In the present study, when the mean severity of OSA was mild, sildenafil proved to be more effective than CPAP as it resulted in a significantly higher rate of successful attempts for intercourse and increased IIEF domain scores compared to CPAP. The direct smooth muscle relaxation in the penile arteries and corpora cavernosa caused by sildenafil may explain the higher effectiveness of this treatment. The higher effectiveness of sildenafil may consequently explain the higher number of intercourse attempts, reflecting the men's strengthened self-confidence. However, the effectiveness of sildenafil in these patients was lower than that generally reported in men with ED, and in a specific study group of men with ED [19, 20]. This may be caused by the combination of smoking abuse and comorbidities, true risk factors for ED, and by the OSA-related hypoxia, though mild, which impairs NO's antioxidant function with adverse vascular consequences. Possibly for these reasons, according to the IIEF domain scores, the men in this study suffered from severe ED. Moreover, the sildenafil-treated patients did not receive specific OSA therapy for three months. Thus, the apnea-induced daytime somnolence and the depressed mood commonly seen in patients with apnea episodes may have negatively affected the quality of life in these individuals [21], not allowing sildenafil to work to its full potential.

The satisfaction with treatment results reported in this study should be interpreted with caution. The small number of studied patients and the mild severity of underlying OSA restricted the satisfaction evaluation. Moreover, the trial was not blind and the different nature of the two treatments might cause bias. However, the differences in efficacies reflect on the patients' and their partners' satisfaction with treatment for ED. It must be emphasized that all patients treated with sildenafil succeeded in at least two attempts at intercourse. Obviously, the patient scores were higher than those of their partners. This finding likely stems from the different perception of treatment satisfaction in patients and partners. Generally, the expectations of women, affected by intimacy and emotional closeness, are substantially different from those of the men, who measure success based on the improvement of the erection. Although sildenafil was more effective than CPAP in treating ED, approximately half of the patients were not satisfied with this treatment. Thus, it seems that none of the studied therapeutic methods met the needs and expectations of all patients. It must be noted that satisfaction was not affected by adverse events, as both therapeutic methods proved to be safe and well tolerated.

In conclusion, the results of this study suggest that both therapeutic methods were safe and effective, but sildenafil was superior to CPAP in the treatment of ED in men with OSA. Because OSA and comorbidities represent a model of severe endothelial dysfunction, they may be associated with severe ED as well. This fact possibly results in a lower effectiveness of sildenafil compared to that generally observed in men seeking treatment for ED. Because of the high percentage of dissatisfaction with both treatments, we conclude that different therapeutic methods, including combinations of CPAP with sildenafil, or newer oral agents, should be studied further.

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**Appendix I**

International Index of Erectile Function. a. is scored with 0; b. with 5; c. with 4; d. with 3; e. with 2; f. with 1.

| Question 3 | Question 4 |
|---|---|
| Over the last month, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? | Over the last month, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? |
| a. Did not attempt intercourse | a. Did not attempt intercourse |
| b. Almost always or always | b. Almost always or always |
| c. Most times (much more than half the time) | c. Most times (much more than half the time) |
| d. Sometimes (about half the time) | d. Sometimes (about half the time) |
| e. A few times (much less than half the time) | e. A few times (much less than half the time) |
| f. Almost never or never | f. Almost never or never |

**Appendix II**

Erectile Dysfunction Inventory of Treatment Satisfaction question 1. a. is scored with 5; b. with 4; c. with 3; d. with 2; e. with 1.

| Patient version | Partner version |
|---|---|
| Overall, how satisfied are you with this treatment? | Overall, how satisfied are you with this treatment for your partner's erection problem? |
| a. Very satisfied | a. Very satisfied |
| b. Somewhat satisfied | b. Somewhat satisfied |
| c. Neither satisfied nor dissatisfied | c. Neutral; neither satisfied nor dissatisfied |
| d. Somewhat dissatisfied | d. Somewhat dissatisfied |
| e. Very dissatisfied | e. Very dissatisfied |


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