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## **Continuous Positive Airway Pressure Therapy in Obstructive Sleep Apnea Patients with Erectile Dysfunction—A meta-analysis**

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### **Abstract**

**Background:** Erectile dysfunction (ED) with obstructive sleep apnea (OSA) is a relatively common issue for men. A number of clinical studies have demonstrated that continuous positive airway pressure (CPAP) therapy may effectively alleviate ED symptom from patients with OSA.

**Methods:** PubMed, MEDLINE, EMBASE and Cochrane Library databases were utilized and searched for the relevant studies up to September 2, 2019. The International Index of Erectile Function 5 (IIEF-5) scoring system from the patients before and after receiving their CPAP therapy were collected according to the strict inclusion and exclusion criteria. REVMAN 5.3 software was applied for the meta-analysis.

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**Results:** A total of seven publications consisted of 206 ED patients with OSA were included in the study. ED patients with OSA received CPAP treatment were significantly improved based on the IIEF-5 scores [Weighted Mean Difference (WMD) = 1.14, 95% confidence interval (CI) = 0.89 – 1.38,  $z=9.09$ ,  $p < 0.0001$ ]. Our research found that the high heterogeneity is mainly due to Zhang's research, because his patient's AHI is much higher than other patients. We removed Zhang's study, a moderate heterogeneity ( $I^2 = 54\%$ ,  $P = 0.05$ ) was found in this study. Our research found that the high heterogeneity is mainly due to Zhang's research, because his patient's AHI is much higher than other patients.

**Conclusion:** The results suggest that continuous positive airway pressure therapy improve erectile dysfunction patients with obstructive sleep apnea. However, further evidence is needed due to the insufficient number of included patients and high heterogeneity.

**Keywords:** Continuous positive airway pressure; obstructive sleep apnea; erectile dysfunction; Meta-analysis.

Abbreviations: AHI, apnea hypopnea index; CI, confidence interval; CPAP, continuous positive airway pressure; ED, erectile dysfunction; IIEF-5, international Index of Erectile Function 5; OSA, obstructive sleep apnea; WMD, weighted mean difference.

## 1. Introduction

Obstructive Sleep Apnea (OSA) is a chronic respiratory condition leading to intermittent hypoxia and disturbances of sleep structure, resulting in partial or complete obstruction of the upper airways <sup>[1,2]</sup>. Epidemiological survey shows that approximately 3%-9% of women and 10%-17% of men have OSA in the United States <sup>[3]</sup>, and around 4.1% people who aged 14 or over have OSA in Guangxi province, China <sup>[4]</sup>. OSA is an important predisposing risk factor for primary hypertension, atherosclerosis, myocardial infarction, cerebral infarction, and stroke. It also significantly affects the quality of life due to its prevalence and severity, and is linked to Erectile Dysfunction (ED). Previous studies indicated that patients with OSA have a higher risk of ED, and nearly half of OSA male patients may already have ED <sup>[5-8]</sup>. The causative factors of ED in the setting of OSA are hypoxemia, hypercapnia, and acid-base decompensation <sup>[9,10]</sup>. Reductions

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of serum testosterone and prolactin levels in patients with OSA are associated with the severity of OSA, and sexual dysfunction is caused mainly by the changes in sex hormones<sup>[11]</sup>. Patients with ED usually receive drug treatments such as Sildenafil, Vardenafil and Tadalafil, however, the ED symptoms may not be able to fully recovered<sup>[12]</sup>, and the treatment itself is expensive<sup>[13]</sup>. Instead of medications, continuous positive airway pressure (CPAP) therapy has been utilised and widely accepted treatment strategy for OSA patients<sup>[14,15,16]</sup>. There are a number of clinical trials have shown that CPAP therapy may relief ED symptoms in men with OSA, but its efficacy has not yet been discussed. Therefore, this meta-analysis aims to collect the International Index of Erectile Function 5 (IIEF-5) data and systematically evaluate the effect of CPAP therapy on male OSA patients with ED symptoms.

## **2. Materials and Methods**

### **2.1. Search strategy**

PubMed, MEDLINE, EMBASE and Cochrane library were utilised and searched for the relevant studies until May 20, 2019. The searching terms included “continuous positive airway pressure”, “CPAP”, “erectile dysfunction”, “ED”, “obstructive sleep apnea”, “obstructive sleep apnea syndrome”, “obstructive sleep apnea-hypopnea syndrome”, and “OSA”. All the data were collected based on peer-reviewed literature, and each of the studies obtained approval from their ethic committees.

### **2.2 Selection criteria**

After the literature search, titles and abstracts of the articles were initially, independently reviewed by two reviewers. Articles that do not satisfy the inclusion criteria were excluded. The potentially relevant articles, or a disagreement between the two reviewers, the full-text articles will be obtained for further evaluation. If the disagreement could not be settled, a third reviewer will be called to resolve the difference. The inclusion criteria were used as follows: 1) study subjects were adult patients diagnosed with OSA and ED; 2) the intervention with CPAP therapy was documented; 3) IIEF-5 score assessment of erectile function was provided; 4) the peer-reviewed

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literature published in English. The exclusion criteria consisted of the follow-up time of less than one-month, duplicate reports, lack of intervention or outcome data, and non-English publications.

### **2.3. Data extraction**

The data were extracted by two reviewers using a unified data extraction table. The recorded data consist of the first author's name, year of publication, study location, sample size, type of study, apnea-hypopnea index (AHI), the IIEF-5 score before and after CPAP treatment, and the length of follow-up. If the article did not describe any of these factors clearly, the authors of the article were contacted for clarification.

### **2.4. Statistical analysis**

Revman(version 5.3) and STATA was used to carry out the meta-analysis. The chi-square test was used to examine heterogeneity, which was quantified with  $I^2$  with the standard of  $\alpha=0.1$ . The heterogeneity between the two studies was defined when  $I^2 > 50\%$  and  $P < 0.1$ . If the heterogeneity was not statistically significant, a random-effect model was applied. Subgroup analysis and meta-regression were used to explore the source of the heterogeneity. Sensitivity was achieved by removing the included studies one by one. Egger's and Begg's tests were used to evaluate publication bias, and  $P < 0.05$  was considered statistical significance.

### **2.5. Evaluating indicator**

The IIEF-5 is a self-administered 5-item questionnaire that measures erectile function. The IIEF was first developed in conjunction with the clinical trial program for sildenafil and has been adopted as the most widely used to measure of ED in clinical settings. Each of the IIEF-5 items is based on a 5-point ordinal scale, and a lower score representing a poorer sexual function. The severity of ED can be classified into 5 categories based on the IIEF-5 scoring system: no ED (22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), and severe (5-7).

## **3. Results**

### **3.1 Study selection and characteristics**

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A total of 149 articles written in English were retrieved. After reviewing the titles, abstracts, and full-texts of the articles, 6 articles<sup>[17-23]</sup> were found to report the effect of CPAP treatment for OSA based on the IIEF-5 questionnaire in men with ED. The total number of subjects from all the included studies was 206. The results of the literature search process are shown in **Figure 1**. The characteristics of the included studies are presented in **Table 1**.

### 3.2. Meta-analysis results

A forest plot of the effects of CPAP treatment on patients with OSA and ED is shown in **Figure 2**. The meta-analysis shows that CPAP therapy significantly increases the IIEF-5 score and improves ED in patients with OSA. The combination of seven studies showed a moderate heterogeneity ( $Chi^2=20.94$ ,  $I^2 = 71\%$ ,  $P = 0.05$ ) and therefore a random-effects model was employed. The differences between two groups (before and after CPAP treatments) was statistically significant (WMD = 1.14, 95%, CI: 0.89– 1.38,  $P < 0.0001$ ).

### 3.3. Results of sensitivity analysis

A sensitivity analysis found the reason for the high heterogeneity. The result is shown in **Table 2**, after removal of Zhang's study, the combination of six studies showed a moderate heterogeneity ( $Chi^2=10.95$ ,  $I^2 = 54\%$ ,  $P = 0.05$ ). Through the analysis of Zhang's study, we found that in Zhang's study, the patients' AHI index was much higher than other studies, which means that the patients in the Zhang's study had more severe apneas, which may be caused heterogeneity. Except for Zhang's research, the included research is deleted one by one to observe the changes of product. A single research has no significant effect on the overall measurement results.

### 3.4. Publication bias

The publish bias analysis shows that the Begg's and Egger's tests have no significant publication bias (Begg's test:  $P = 0.881$ ; Egger's test:  $P = 0.873$ ). Meanwhile, the funnel chart shows that the results of this analysis are relatively reliable (in Figure 3).

## 4. Discussion

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CPAP is an internationally recognized treatment for OSA patients, but there is no discussion of OSA patients with ED symptom. Therefore, in this meta-analysis, we found that CPAP therapy could be an effective treatment strategy for ED in OSA patients. ED is commonly found in patients with OSA, and both OSA and ED endanger the physical and mental health in middle-aged and elderly males<sup>[7]</sup>. At present, the mechanism of OSA patients encountered with sexual dysfunction remains controversial. OSA patients with nocturnal intermittent hypoxia cause peripheral nerve axon and myelin sheath lesion and block/delay neural signal transmission. Consequently, patients usually experience with extended reaction time for the corpus cavernosum reflex, resulting in an obstacle of the penile erectile function. The nocturnal hypoxemia, hypercapnia and disorder sleep structure in these patients may damage the vascular endothelial cells and reduce nitric oxide (NO) synthesis, resulting in a decrease conversion of guanosine monophosphate (GMP) to cyclic GMP (cGMP) synthesis in the smooth muscle cells<sup>[22]</sup>. The decrease of intracellular cGMP concentration causes the contraction of smooth muscle and reduce the blood flow into the penis that leads to the penis softens.

There are several treatments are available for ED patients with OSA. Drug therapy using Sildenafil, Tadalafil or Avanafil is relatively expensive. Also, a certain number of patients respond to this treatment poorly. Surgery is another option. However, due to the lack of long-term follow-up data, the outcome remains uncertain<sup>[24]</sup>. The increasing number of studies shown that the levels of serum testosterone and prolactin in the OSA patients are associated with the severity of sleep apnea<sup>[25,26]</sup> and therefore CPAP therapy is recommended. Perimenis *et al.*<sup>[17,18]</sup> found that CPAP therapy significantly increases NO and nitric oxide synthase (NOS) levels in serum from patients with OSA, the reduction of both NO and NOS is normally considered the cause of sexual dysfunction in the patients with OSA.

It has been suggested that the IIEF-5 questionnaire can be used to evaluate OSA patients with ED<sup>[27]</sup> as an effective and psychological tool. The questionnaire has been translated into multiple languages and become an internationally accepted self-assessment questionnaire for ED patients screening. Gambineri *et al.*<sup>[28]</sup> reported that the IIEF-5 scoring system and the levels of serum sex hormone are negatively correlated with AHI, and positively with arterial oxygen saturation

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(SaO<sub>2</sub>). Thus, the IIEF-5 questionnaire can be used to evaluate the severity of ED and to estimate the effect of CPAP therapy for male OSA patients with ED [27]. The meta-analysis here has shown that the CPAP therapy significantly improved the IIEF-5 scoring in OSA patients treated with CPAP, based on a total of seven included studies comprising 206 patients (WMD = 3.70, 95% CI: 2.38 - 5.02,  $P < 0.001$ ), Zhang's study is the largest, but due to the high AHI of patients, it has a relatively large impact on heterogeneity, so we removed Zhang's study. We found that removing other studies did not have much impact on heterogeneity. Further analysis indicated that the length of follow-up contributed to the observed heterogeneity.

For example, Perimenis *et al.* [17] recruited 15 ED patients with OSA symptoms (AHI: 7.3±1.2) to compare treatment response by the drug sildenafil with CPAP therapy in a randomized control trial study. Their study also showed a moderate heterogeneity in this meta-analysis.

The responses of CPAP treatment can be considered to be immediate and continuous ones, and the treatment for 1-month to 3-month is a short period. After the patients received their CPAP treatments, Perimenis *et al.* [17,18] noticed that OSA symptoms, including snoring and daytime sleepiness, were relieved, and the sleeping quality was improved. They also observed that the clinical indicators, including AHI, sleep structure, and sleep hypoxia, were well-recovered. This finding was confirmed by Grunstein *et al.* [29] and demonstrated that a 3-month or longer CPAP therapy, could maximize the treatment benefits, and improve the levels of the testosterone and sex hormone-binding proteins on male OSA patients.

## 5. Conclusion

Previously, a number of researchers paid attention to study the relationship between OSA and ED while a small number of participants from each study was not able to draw a conclusive conclusion. Utilizing the IIEF-5 scoring system in this meta-analysis found that CPAP therapy is effectively relief the ED symptoms for male OSA patients with ED in a 3-month length setting. Long-term CPAP therapy may be needed for further evaluation.

## AUTHOR CONTRIBUTION

Designing research/study: Guodong DU , Lei Ma.

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Performing research/study: Zhihao Yang, Guodong DU.

Data: Yang Zhao, Yunhui Lv, Tung On Yau.

Analyzing Data: Zhihao Yang, Tung On Yau.

Writing the paper: Zhihao Yang, Guodong DU, Yang Zhao.

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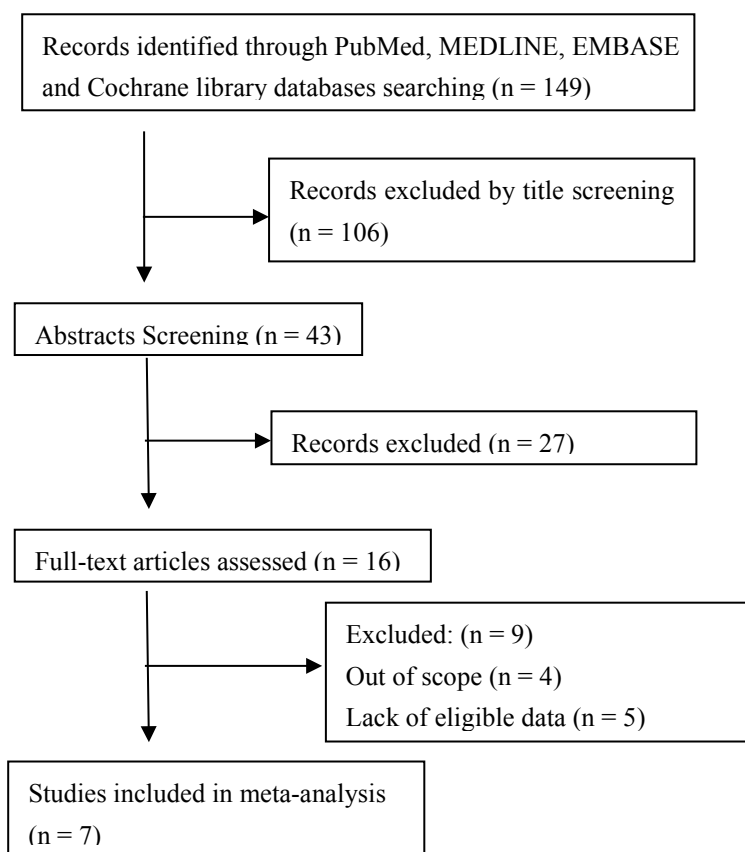
**Table 1. Characteristics of the patients with the CPAP treatment in each included study( n = 206)**

Author	Year	Country	No.of patients	Age (MEAN±SD)	Follow-up Duration (Month)	Daily duration	Study	AHI (MEAN±SD)	IIEF-5 Score	
									Pre-CPAP (MEAN±SD)	Post-CPAP (MEAN±SD)
Perimenis <i>et al.</i> <sup>16</sup>	2004	Greece	15	55.7±3.6	3	NR	RCT	7.3±1.2	21.7±4.9	27.3±8.6
Perimenis <i>et al.</i> <sup>17</sup>	2007	Greece	20	55.5 (48-62) <sup>†</sup>	3	NR	RCT	NR	7±1.9	10.8±4.4
Taskin <i>et al.</i> <sup>18</sup>	2010	Turkey	17	51.05±7.28	1	7 h/day	SCT	35±19.3	15.71±5.12	19.06±3.94
Pastore <i>et al.</i> <sup>19</sup>	2014	Italy	41	48.6±8.5	3	NR	RCT	47.3±14.9	7.4±1.4	11.7±3.7
Husnu <i>et al.</i> <sup>20</sup>	2015	Turkey	28	48.85±10.96	3	NR	SCT	19.84±5.66	16.63±5.91	20.92±6.79
Zhang <i>et al.</i> <sup>21</sup>	2016	China	53	43.87±9.17	3	6.8 h/day	SCT	63.45±12.03	18.21±4.05	19.21±3.86
Li <i>et al.</i> <sup>22</sup>	2016	China	32	55.5±7.2	1	5.8 h/day	SCT	51.6±16.3	14.2±2.9	19.2±3

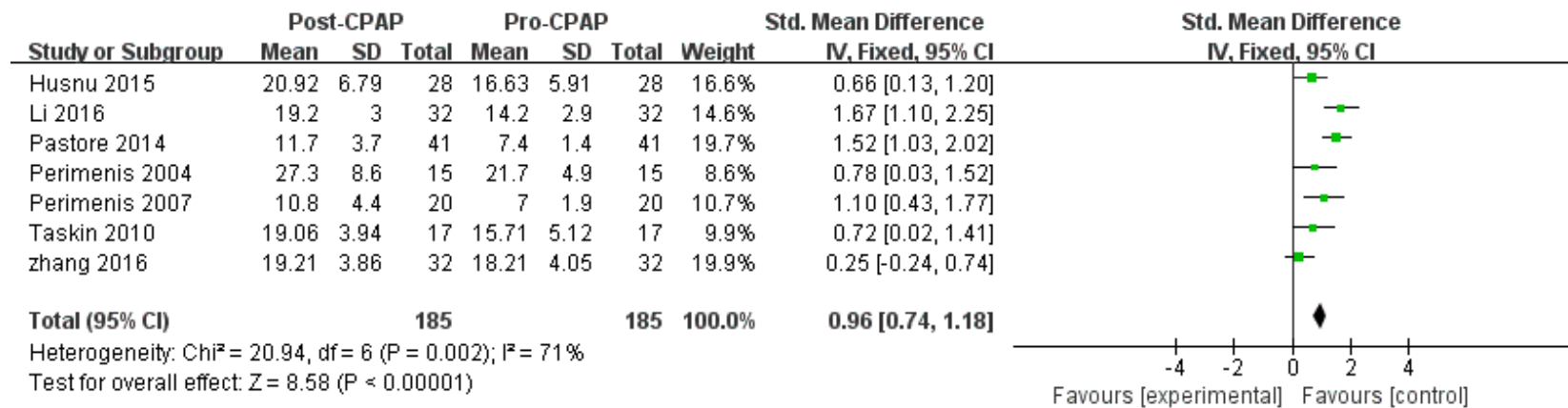
NR: not reported; SCT: self-controlled trails; RCT: randomized controlled trails ; AHI: apnea-hypopnea index;IIEF-5:international index of erectile function-5;NR:no report <sup>†</sup>: Data expressed as median (range)

**Table 2. Sensitivity analysis on heterogeneity**

Remove study	$\chi^2$	$I^2$	$P$
Zhang <i>et al.</i> <sup>21</sup>	10.95	54%	0.05
Perimenis <i>et al.</i> <sup>16</sup>	25.27	80%	0.05
Perimenis <i>et al.</i> <sup>17</sup>	25.27	80%	0.05
Taskin <i>et al.</i> <sup>18</sup>	25.11	79%	0.05
Pastore <i>et al.</i> <sup>19</sup>	17.53	76%	0.05
Husnu <i>et al.</i> <sup>20</sup>	24.62	80%	0.05
Li <i>et al.</i> <sup>22</sup>	16.95	75%	0.05

**Fig 1. Flow diagram of the literature search for meta-analysis**

**Figure 2. Forest plot illustrating the effect of CPAP treatment in obstructive sleep apnoea patients with erectile dysfunction. The vertical dotted line through the centre of the diamond and graph represents the overall estimated relative risk. WMD, weighted mean difference.**



**Figure 3 Funnel plots of publication bias**