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CLINICAL REVIEW

The effect of CPAP and PDE5i on erectile function in men with obstructive sleep apnea and erectile dysfunction: A systematic review and meta-analysis

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SUMMARY

Growing evidence has shown that obstructive sleep apnea (OSA) and erectile dysfunction (ED) often coexist. However, the effect of continuous positive airway pressure (CPAP) on erectile function remains controversial. The objective of this review was to clarify the anti-ED effect of CPAP and further compare the efficacy between CPAP, phosphodiesterase type 5 inhibitors (PDE5i) and combination therapy on erectile function in OSA patients concurrent ED. Literature search was performed up to December 1st, 2018 and 26 studies were included in the review. Results showed that CPAP significantly ameliorated the international index of erectile function (IIEF) score, total erectile events (TEE) and nocturnal penile rigidity (NPR), while no significant improvements in nocturnal penile tumescence circumference (NPTC). Moreover, CPAP was inferior to PDE5i in improving IIEF-erectile function, IIEF-intercourse satisfaction, NPTC, successful attempted intercourses rate (SAIR) and erectile dysfunction inventory of treatment satisfaction-question one (EDITS-Q1), while CPAP and PDE5i were of equal efficacy in other domains of IIEF and NPR. Interestingly, CPAP was more effective in improving TEE. Furthermore, CPAP combined with PDE5i was superior to CPAP alone in improving IIEF score, SAIR, and TEE. This review provided promising insights about CPAP-based ED treatment for OSA patients.

Introduction

Obstructive sleep apnea (OSA) is defined as sleep fragmentation and recurrent reductions of oxygen saturation caused by repetitive upper airway collapse during sleep. Previous study has reported that estimated 10% of middle-aged men were affected by OSA [1]. Moderate to severe OSA was found to be closely related to the increased risk of neurobehavioral and cardiovascular events [2,3]. Erectile dysfunction (ED), characterized by persistent inability to attain and maintain a sufficient erection for reaching sexual satisfaction, is considered as an early sign of nerve involvement and cardiovascular disease [4,5]. Accumulated evidence has demonstrated that OSA and ED often coexist. 50–80% of OSA patients were concurrent with ED [6–8], which indicated that either of two diseases should be considered whenever the other is diagnosed.

Continuous positive airway pressure (CPAP) has been extensively used as the standard therapy for OSA. Emerging studies have found that CPAP significantly improved the erectile function in OSA patients concurrent ED [9–11]. However, Zhang et al. and Shin et al. reported no significant differences in the 5-item international index of erectile function (IIEF-5) after CPAP intervention [12,13]. Thus, the effect of CPAP on erectile function in men with OSA and ED remains controversial. Phosphodiesterase type 5 inhibitors (PDE5i), as the first-line therapy of ED, has shown great effectiveness for the treatment of OSA patients concurrent ED [14,15]. Recently, several randomized controlled trials (RCT) have investigated the efficacy of CPAP versus PDE5i on erectile function [5,14–16]. However, small sample size makes conclusions far from persuasive. Furthermore, the combination of CPAP and PDE5i seems to be promising for the treatment of ED in OSA patients

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Abbreviations

AHI	apnea hypopnea index
CI	confidence interval
CPAP	continuous positive airway pressure
ED	erectile dysfunction
EDITS-Q1	erectile dysfunction inventory of treatment satisfaction-question one
IIEF	international index of erectile function
IIEF-5	5-item international index of erectile function
IIEF-EF	international index of erectile function - erectile function
IIEF-IS	international index of erectile function-intercourse satisfaction
IIEF-OF	international index of erectile function-orgasmic function
IIEF-OS	international index of erectile function-overall satisfaction
IIEF-SD	international index of erectile function-sexual desire
NPR	nocturnal penile rigidity
NPT	nocturnal penile tumescence
NPTC	nocturnal penile tumescence circumference
OSA	obstructive sleep apnea
PDE5i	phosphodiesterase type 5 inhibitors
RCT	randomized controlled trial
REM	rapid eye movement
RR	relative risk
SAIR	successful attempted intercourses rate
SMD	standardized mean difference
TEE	total erectile events
WMD	weighted mean difference

[4,17,18], thus a systematic review is needed as the reference for the future clinical researches.

The objective of the present review was to clarify the effect of CPAP on erectile function and further evaluate the efficacy of CPAP, PDE5i and their combination therapy on erectile function in men with OSA and ED, which was expected to provide conclusive evidence for the clinical intervention of the OSA patients concurrent ED. (see Table 1).

Material and methods

Search strategy

The study was performed based on the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) guideline [19,20] (Table S1). We registered the protocol of this systematic review on PROSPERO (Record: CRD42019119046). We performed a systematic literature search in databases of PubMed, Embase, and Web of Science from July 1st, 1987 to December 1st, 2018. The search strategy was the combination of the following terms: (obstructive sleep apnea) AND (erectile dysfunction) AND (continuous positive airway pressure). The restriction of 'Title/abstract' was not adopted in the search strategy to avoid the omission of literature. Detailed search strategy was listed in Table S2.

Inclusion and exclusion criteria

The studies meeting the following criteria were enrolled in the present systematic review: 1) evaluated the effect of CPAP on erectile function in men with OSA and ED; 2) compared the efficacy between CPAP, PDE5i and PDE5i combined with CPAP on erectile function in men with OSA and ED; 3) IIEF-5 or IIEF-15 as the primary outcome. Erectile dysfunction inventory of treatment satisfaction-question one (EDITS-Q1), successful attempted intercourse rate (SAIR), nocturnal penile rigidity (NPR), nocturnal penile tumescence circumference (NPTC) and total erectile events (TEE) as the second outcomes. Studies reported at least one of the above outcomes; 4) RCT or observational (pre-post) studies. Studies were excluded whenever the following happened: 1) reviews or case reports; 2) animal experiments; 3) studies without publishing ED-related outcomes.

Data collection and management

Two researchers (Li ZY and Zhu SQ) reviewed eligible studies independently. Disagreements were settled by consensus. We extracted the following items from the original studies: 1) baseline features: author, publication year, design, studied population, sample size, mean age, OSA severity, ED severity; 2) interventions: OSA treatment, ED treatment, duration of treatment, adjusted confounders; 3) outcomes: IIEF-5, IIEF-15, IIEF-erectile function (IIEF-EF), IIEF-intercourse satisfaction (IIEF-IS), IIEF-orgasmic function (IIEF-OF), IIEF-sexual desire (IIEF-SD), IIEF-overall satisfaction (IIEF-OS), EDITS-Q1 score, SAIR, NPR, NPTC and TEE. When the necessary data of some studies were incomplete, the first author and corresponding author were contacted.

Risk of bias evaluation and quality assessment

Two researchers (Zhu SQ and Fang ZQ) independently evaluated the quality of eligible studies. RCT studies were evaluated based on the Cochrane Risk of Bias tool in RevMan Version 5.3 [21,22]. Non-RCT studies were assessed according to the risk of bias assessment tool for non-randomized studies (RoBANS) [23]. The quality of evidence was evaluated by the GRADEpro software and GRADE assessment [22,24]. The discrepancies were settled by the discussion of all the authors.

Statistical analysis

The mean and its standard deviation were pooled to estimate the effect of CPAP and/or PDE5i on erectile function in men with OSA and ED. We evaluated the effect sizes of continuous outcomes using weighted mean difference (WMD) with its 95% confidence interval (CI). When the measure units of pooled studies were inconsistent, standardized mean difference (SMD) with corresponding 95% CI was used. As regards to dichotomous outcome, RR and corresponding 95% CI were obtained to evaluate the outcome effects. Q-test and I^2-statistics were adopted to assess the between-studies heterogeneity. $I^2 > 50\%$ and $P < 0.1$ were regarded as significant heterogeneity. Random-effects model was employed when heterogeneity was significant. Sources of heterogeneity were explored using pre-specified subgroup analysis. Besides, sensitivity analysis was implemented to evaluate the influence of individual study on pooled results. Publication bias was detected by the

Table 1
The characteristics of included studies.

Authors, year	Design	Studied population	Sample size	Mean age (year)	OSA severity	ED severity	OSA treatment	ED treatment	Duration of treatment	Outcomes on ED	Adjusted confounders	
											ED-related diseases	ED-related interventions
Karacan et al., 1995 [29]	Prospective observational	OSA with ED	22	54	All levels	All levels	CPAP	None	NR	TEE,NPR,NPTC	Not adjusted	Not adjusted
Li et al., 2004 [9]	RCT	OSA with ED	CPAP *vs* Contol: 15 *vs* 12	39.8	All levels	All levels	CPAP	None	4 wk	IIEF-5	Not adjusted	Not adjusted
Perimenis et al., 2004 [15]	RCT	OSA with ED	CPAP *vs* Sildenafil: 15 *vs* 15	CPAP *vs* Sildenafil: 55.7 *vs* 56.4	Mild	Severe	CPAP	100 mg sildenafil on demand	12 wk	SAIR, IIEF-15	Adjusted	Adjusted
Margel et al., 2005 [33]	Retrospective observational	OSA with ED	60	53.9–59	All levels	All levels	CPAP	None	Median 17 mo	IIEF-5	Adjusted	Adjusted
Perimenis et al., 2007 (1) [16]	RCT	OSA with ED	CPAP *vs* Sildenafil: 20 *vs* 20	CPAP *vs* Sildenafil: 55.5 *vs* 55.3	Mild	Severe	CPAP	100 mg sildenafil on demand	12 wk	SAIR, IIEF-EF,EDITS-Q1	Adjusted	Adjusted
Perimenis et al., 2007 (2) [4]	RCT crossover	OSA with ED	CPAP + Sildenafil *vs* CPAP: 40 *vs* 40	56.2	Mild to moderate	All levels	CPAP	100 mg sildenafil on demand	12 wk	SAIR	Adjusted	Adjusted
Hussein et al., 2009 [18]	RCT	OSA with ED	CPAP + **S**ildenafil *vs* CPAP: 18 *vs* 18	28–60	All levels	All levels	CPAP	50 mg Sildenafil daily	4 wk	IIEF-EF	Not adjusted	Not adjusted
Yang et al., 2009 [30]	Prospective observational	OSA with ED	22	NR	All levels	All levels	CPAP	None	12 wk	IIEF-5	Adjusted	Adjusted
Papadimitriou et al., 2010 [17]	RCT	OSA with ED	CPAP + Tadalail *vs* CPAP: 11 *vs* 11	NR	All levels	All levels	CPAP	5 mg tadalafil daily	12 wk	IIEF, TEE, NPT	Adjusted	Adjusted
Taskin et al., 2010 [34]	Prospective observational	OSA	17	51.05	severe	All levels	CPAP	None	4 wk	IIEF-5	Adjusted	Adjusted
Dombrowsky et al., 2012 [32]	Prospective observational	OSA	NR	45.8	All levels	All levels	CPAP	None	24 wk	IIEF-EF	NR	NR
Khafagy et al., 2012 [28]	Prospective observational	OSA with ED	80	41.9	Mild	All levels	CPAP	None	12 wk	IIEF-5, NPR	Adjusted	Adjusted
Budweiser et al., 2013 [38]	Prospective observational	OSA with ED	CPAP *vs* Contol: 21 *vs* 18	NR	All levels	moderate to severe	CPAP	None	Mean 36.5 mo	IIEF-15	Not adjusted	Not adjusted
Shin et al., 2013 [12]	Prospective observational	OSA	16	52.8	severe	All levels	CPAP	None	28 wk	IIEF-5	Adjusted	Adjusted
Knapp et al., 2014 [35]	Prospective observational	OSA	25	65.4	Moderate to severe	All levels	CPAP	None	12 wk	IIEF-5	Not adjusted	Not adjusted
Pastore et al., 2014 [14]	RCT	OSA with ED	CPAP *vs* Sildenafil: 41 *vs* 41	CPAP *vs* Sildenafil: 48.6 *vs* 47.4	severe	Moderate to severe	CPAP	100 mg sildenafil on demand	12 wk	IIEF-EF, EDITS-Q1, SAIR	Adjusted	Adjusted
Sekiguchi et al., 2014 [36]	Retrospective observational	OSA with ED	30	NR	All levels	All levels	CPAP	None	24 wk	IIEF-5	Not adjusted	NR
Husnu et al., 2015 [27]	Prospective observational	OSA	28	NR	All levels	All levels	CPAP	None	12 wk	IIEF-5	Adjusted	Adjusted
Acar et al., 2016 [10]	Prospective observational	OSA with ED	21	47	Moderate to severe	All levels	CPAP	None	12 wk	IIEF-15	Adjusted	Adjusted
Daskalopoulou-Vlahogianni et al., 2016 [37]	Retrospective observational	OSA	130	NR	All levels	All levels	CPAP	None	48 wk	IIEF	Not adjusted	NR
Li et al., 2016 [11]	Prospective observational	OSA with ED	32	NR	severe	All levels	CPAP	None	4 wk	IIEF-5	Adjusted	Adjusted
Zhang et al., 2016 [13]	Prospective observational	OSA with ED	53	43.9	severe	All levels	CPAP	None	12 wk	IIEF-5	Adjusted	Adjusted
Irer et al., 2018 [26]	Prospective observational	OSA with ED	54	NR	Moderate to severe	All levels	CPAP	None	12 wk	IIEF-15	Adjusted	Adjusted
Melehan et al., 2018 [5]	RCT factorial design	OSA with ED	CPAP *vs* Sildenafil: 12 *vs* 20	52.6–56.9	Moderate to severe	All levels	CPAP	10 mg vardenafil daily	12 wk	IIEF-15,TEE,NPR,NPTC	Adjusted	Adjusted

(*continued on next page*)

Table 1 (*continued*)

Authors, year	Design	Studied population	Sample size	Mean age (year)	OSA severity	ED severity	OSA treatment	ED treatment	Duration of treatment	Outcomes on ED	Adjusted confounders	
											ED-related diseases	ED-related interventions
Pascual et al., 2018 [25]	RCT	OSA with ED	CPAP *vs* Contol: 30 *vs* 27	54.8	Moderate to severe	All levels	CPAP	None	12 wk	IIEF-15	Adjusted	Adjusted
Schulz et al., 2018 [31]	Prospective observational	OSA	94	51,5	severe	All levels	CPAP	None	6–12 wk	IIEF-5	Not adjusted	Not adjusted

The severity of OSA was rated as mild (AHI = 5–15 events/h), moderate (AHI = 15–30 events/h), and severe (AHI≥30 events/h). The severity of ED was rated as mild (IIEF-EF = 17–25 or IIEF-5 = 12–21), moderate (IIEF-EF = 11–16 or IIEF-5 = 8–11), and severe (IIEF-EF≤10 or IIEF-5≤7).

AHI = apnea hypopnea index; CPAP = continuous positive airway pressure; ED = erectile dysfunction; ESS = Epworth sleepiness scale; IIEF = international index of erectile function; IIEF-EF = international index of erectile function-erectile function; IIEF-5 = 5-item international index of erectile function; IIEF-15 = 15-item international index of erectile function; NPR = nocturnal penile rigidity; NPT = nocturnal penile tumescence; NPTC = nocturnal penile tumescence circumference; NR = not reported; OSA = obstructive sleep apnea; PDE5i = phosphodiesterase type 5 inhibitors; RCT = randomized controlled trial; SAIR = successfull attempted intercourses rate; TEE = total erectile events.

Egger's weighted regression test. All statistical analyses were conducted by STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics

Stepwise search procedures were exhibited in Fig. 1. Database search retrieved 223 relevant studies and 38 studies were subjected to full-text review. Six studies were excluded due to the lack of ED-related outcomes. Four studies and two studies were excluded because of the lack of eligible control and duplicated publication respectively. Subsequently, 26 articles met the inclusion criteria and were included in this systematic review. Of them, nine articles were RCT studies [4,5,9,14–18,25] and 17 articles were observational (pre-post) studies [10–13,26–38]. The majority of the studies were published after 2012. The included studies recruited patients with OSA and ED except seven observational studies reporting OSA population [12,27,31,32,34,35,37]. The severity of OSA in eligible studies was categorized into mild OSA [15,16,28], mild to moderate OSA [4], moderate to severe OSA [5,10,25,26,35], severe OSA [11–14,31,34], and OSA with all levels of severity [9,17,18,27,29,30,32,33,36–38]. Besides, two trials reported severe ED [15,16] and another two investigated moderate to severe ED [14,38], while the remaining studies reported ED with all levels of severity. The majority of studies reported a 12-week therapeutic intervention time. While in three studies, the duration of treatment was more than one year [33,37,38]. Of the 26 studies, 17 studies adjusted the confounders of ED-related diseases and interventions [4,5,10–17,25–28,30,33,34]. Moreover, 11 studies clearly investigated the effect of CPAP on OSA [5,9,11,12,18,28,29,31,32,34,35], and all of them reported a significant improvement on the OSA-related indicators (Table S3). Eventually, 17 studies were further enrolled in the meta-analysis [5,9–16,25–30,33,34].

Study quality and risk of bias

RCT studies were assessed by Cochrane Risk of Bias tool in RevMan Version 5.3. Of nine RCTs, randomization procedures were performed in six trials [4,5,14–16,25] and allocation concealment was implemented in two studies [5,25]. The included studies largely did not conduct blinding and were open-label trials except one study [5]. All the trials were identified as low risk of bias for incomplete outcome data and selective reporting. No explicit other bias was detected in all the studies (Figure S1 and S2). As for the non-RCT studies, RoBANS tool was adopted. Seven studies had high risk of bias in selection of participants for retrospective design [33,36,37] or lack of consecutive recruitment [10,27–29]. Due to insufficient adjustment for ED-related diseases and interventions, the risk of bias regarding confounding variables was high in six trials [29,31,35–38]. Four studies had high risk of bias in measurement of exposure for the inadequate description of CPAP usage [12,27,29,30]. Only two trials reported sufficient blinding of outcome assessments [27,34]. As for the incomplete outcome data, high risk of bias was identified in one study [33]. All studies showed a low risk of bias in relation to selective outcome reporting (Table S4).

The effect of CPAP on erectile function in men with OSA and ED

Four RCT studies [5,9,17,25] and 11 observational studies [10–13,26–30,33,34] including 520 patients had investigated the effect of CPAP on erectile function and were included into the meta-analysis. All outcome measures were evaluated as 'Very low' in

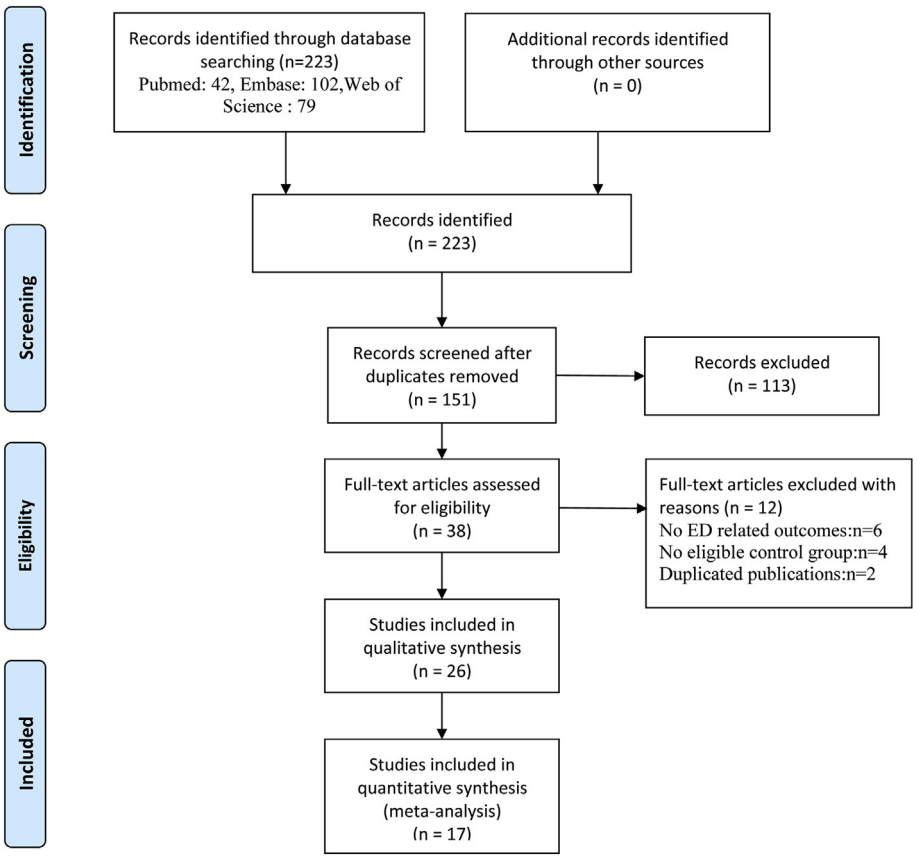

Fig. 1. Flow diagram of study selection. ED = erectile dysfunction.

GRADE assessment other than the effect of CPAP on IIEF-EF in pre-post comparison which was 'Low' (Table S5). As illustrated in Fig. 2A, IIEF-5 score in CPAP group was significant higher than that in non-CPAP group (WMD: 7.40, 95% CI: 3.95–10.85, $P < 0.001$). Similarly, pooled data for IIEF-5 from pre-post studies showed the consistent result (WMD: 3.07, 95% CI: 1.58–4.57, $P < 0.001$, $I^2 = 74.5\%$; Fig. 2B). Besides, CPAP group had higher IIEF-EF score than non-CPAP group despite without statistical significance (WMD: 5.57, 95% CI: −1.82–12.96, $P = 0.14$, $I^2 = 68.4\%$; Fig. 2C). Pooled data for IIEF-EF from pre-post studies indicated that CPAP could obviously increase IIEF-EF score (WMD: 6.98, 95% CI: 5.33–8.62, $P < 0.001$, $I^2 = 0.0\%$; Fig. 2D). Moreover, one sham-controlled trial [5] reported that compared to the sham CPAP users, CPAP users experienced an obvious improvement in TEE (mean: 1.71, 95% CI: 0.51–2.92), however without significant effect in NPR (mean: 1.07, 95% CI: −41.78 to 43.93) and NPTC (mean: −8.50, 95% CI: −41.97 to 24.98). According to the pre-post comparisons, CPAP remarkably increased TEE (WMD: 0.90, 95% CI: 0.32–1.47, $P = 0.002$, $I^2 = 28.5\%$; Fig. 2E) and NPR (SMD: 0.64, 95% CI: 0.17–1.11, $P = 0.007$, $I^2 = 0\%$; Fig. 2F), whereas had no significant effect on NPTC (SMD: 0.31, 95% CI: −0.15–0.77, $P = 0.189$, $I^2 = 0\%$; Fig. 2G).

Six observational studies, which excluded from quantitative analysis for insufficient data, also explored the effect of CPAP on erectile function [31,32,35–38]. Five trials showed that CPAP ameliorated the IIEF score (all $P < 0.05$) in OSA patients [31,32,35,37,38], whereas one trial reported IIEF score decreased in 53.3% of ED patients after CPAP [36]. Interestingly, Schulz et al. [31] founded that the mean changes of IIEF-5 after CPAP were significantly higher in severe ED patients than that in moderate and mild ED patients (7.0 for severe ED; 3.5 for moderate ED; −0.1 for mild ED). Similarly, Shin et al. [12] proposed that the baseline IIEF-5 score was negatively correlated with the improvement of ED (regression coefficient = −0.404, $P = 0.003$).

As for the long-term effect of CPAP on erectile function, the results of three studies were summarized [33,37,38]. Budweiser et al. demonstrated that CPAP significantly improved the total IIEF-15 score as well as IIEF-OF, IIEF-SD, and IIEF-OS in men with moderate to severe ED (all $P < 0.05$) [38]. Likewise, another controlled study founded a remarkable improvement in IIEF after CPAP ($P < 0.001$) [37]. Notably, this study revealed that diabetes served as negative prognostic factors for the improvement of erectile function caused by CPAP, while hypertension as the positive prognostic factor. However, a retrospective study from Margel et al. reported 20% of patients (group 2) showed an improved IIEF-5 score, while 18% (group 3) had a worse score [33]. Besides, the CPAP use in group 2 was significantly higher than that in group 3 (41.2 ± 5.2 h per week vs 31.2 ± 4.8 h per week).

The efficacy of CPAP versus PDE5i on erectile function in men with OSA and ED

Four RCT studies compared the efficacy of CPAP and PDE5i on erectile function in OSA patients concurrent ED [5,14–16]. The outcomes of IIEF-EF, IIEF-IS, IIEF-SD, EDITS-Q1 patient, EDITS-Q1 partner score were evaluated as 'Low' in GRADE assessment, while the outcome of SAIR as 'Moderate'. The remaining outcomes received 'Very low' GRADE assessment scores (Table S5). As shown in Fig. 3A and B, the patients in CPAP group had significant lower IIEF-EF score (WMD: 5.03, 95% CI: 2.01–8.05, $P = 0.002$, $I^2 = 64.9\%$, random-effects) and IIEF-IS score (WMD: 1.41, 95% CI: 0.24–2.59, $P = 0.019$, $I^2 = 33.9\%$, fixed-effects) compared to that in PDE5i

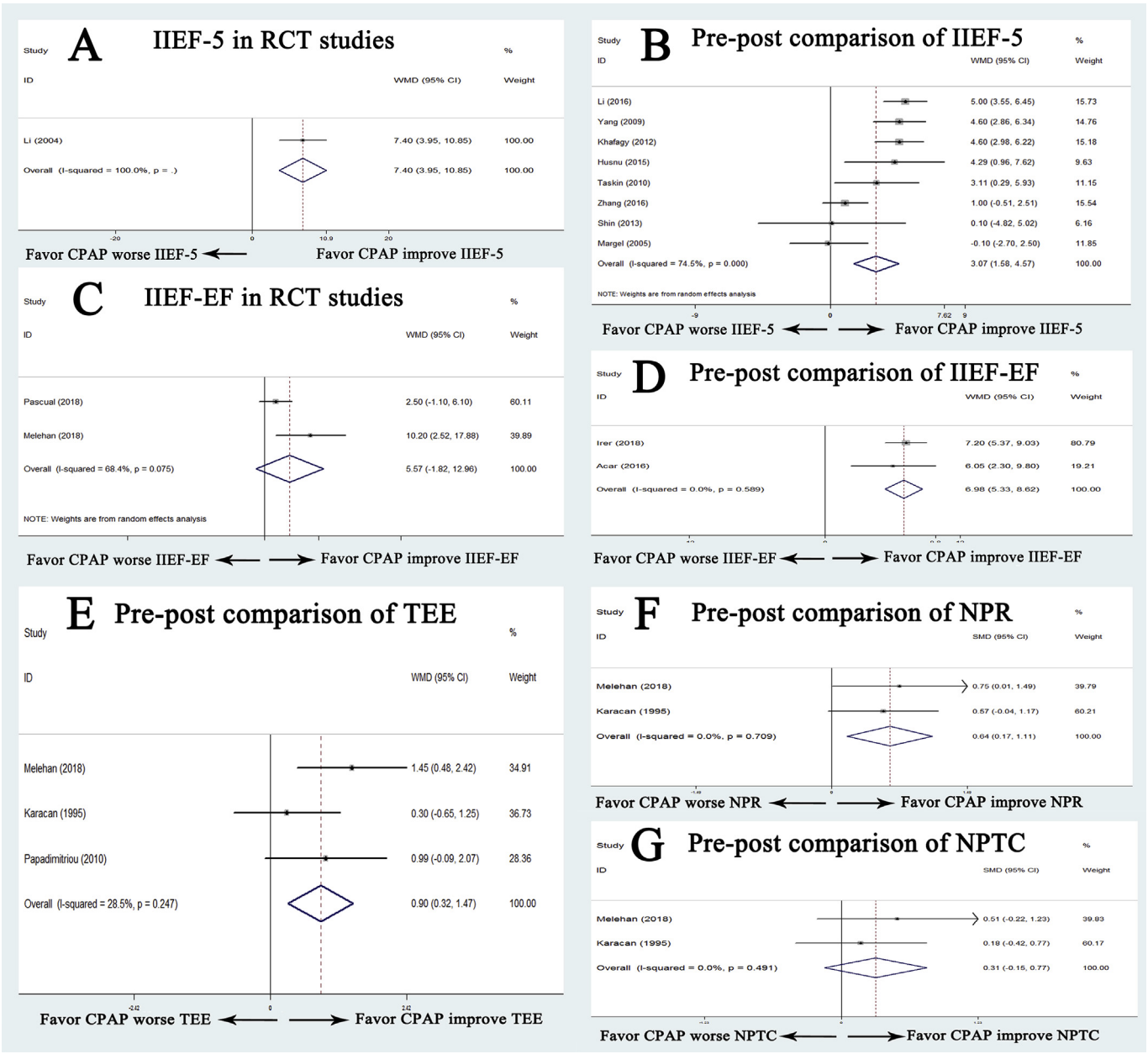

Fig. 2. Effect of CPAP on the IIEF score, TEE, NPR and NPTC in OSA patients. CI = confidence interval; CPAP = continuous positive airway pressure; IIEF = international index of erectile function; IIEF-5 = 5-item international index of erectile function; IIEF-EF = international index of erectile function - erectile function; NPR = nocturnal penile rigidity; NPTC = nocturnal penile tumescence circumference; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SMD = standardized mean difference; TEE = total erectile events; WMD = weighted mean difference.

group. No differences were found in IIEF-OS, IIEF-OF, IIEF-SD and total IIEF score between CPAP group and PDE5i group (Fig. 3C–F). However, according to the placebo-based study of Melehen et al. [5], CPAP was less effective than PDE5i in improving NPTC (WMD: 35.72, 95% CI: 3.26–68.18), whereas more effective than PDE5i in improving the TEE (WMD: −1.88, 95% CI: −3.19–−0.57). No significant differences were found in IIEF score and NPR (Table S6). Furthermore, two trials reported EDITS-Q1 and three trials investigated SAIR. EDITS-Q1 refers to the question: 'Overall, how satisfied are you with this treatment?' [39]. Pooled results indicated that compared to CPAP group, PDE5i remarkably improved the EDITS-Q1 patient score (WMD: 1.24, 95% CI: 0.67–1.80, $P < 0.001$, $I^2 = 0\%$), EDITS-Q1 partner score (WMD: 1.23, 95% CI: 0.76–1.70, $P < 0.001$, $I^2 = 0\%$) and SAIR (RR: 1.97, 95% CI: 1.74–2.22, $P < 0.001$, $I^2 = 0\%$; Fig. 4).

The effect of PDE5i combined with CPAP on erectile function in men with OSA and ED

Three RCT studies investigated the effect of PDE5i combined with CPAP on erectile function in OSA patients concurrent ED [4,17,18]. Papadimitriou et al. [17] reported that compared to CPAP alone, CPAP plus 5 mg tadalafil had higher IIEF score (21.18 ± 7.37 vs. 25.7 ± 5.01) despite without statistical significance. No differences were found between two groups in TEE (2.45 ± 1.44 vs. 2.3 ± 0.95). Similarly, another trial [18] found that PDE5i (50 mg Sildenafil daily) combined with CPAP obviously improved IIEF score and TEE compared to CPAP alone. Besides, Perimenis et al. [4] reported that compared to CPAP alone, PDE5i (100 mg sildenafil on demand) combined with CPAP significantly ameliorated the SAIR (61.1% vs. 24.8%) with 70% satisfaction in studied

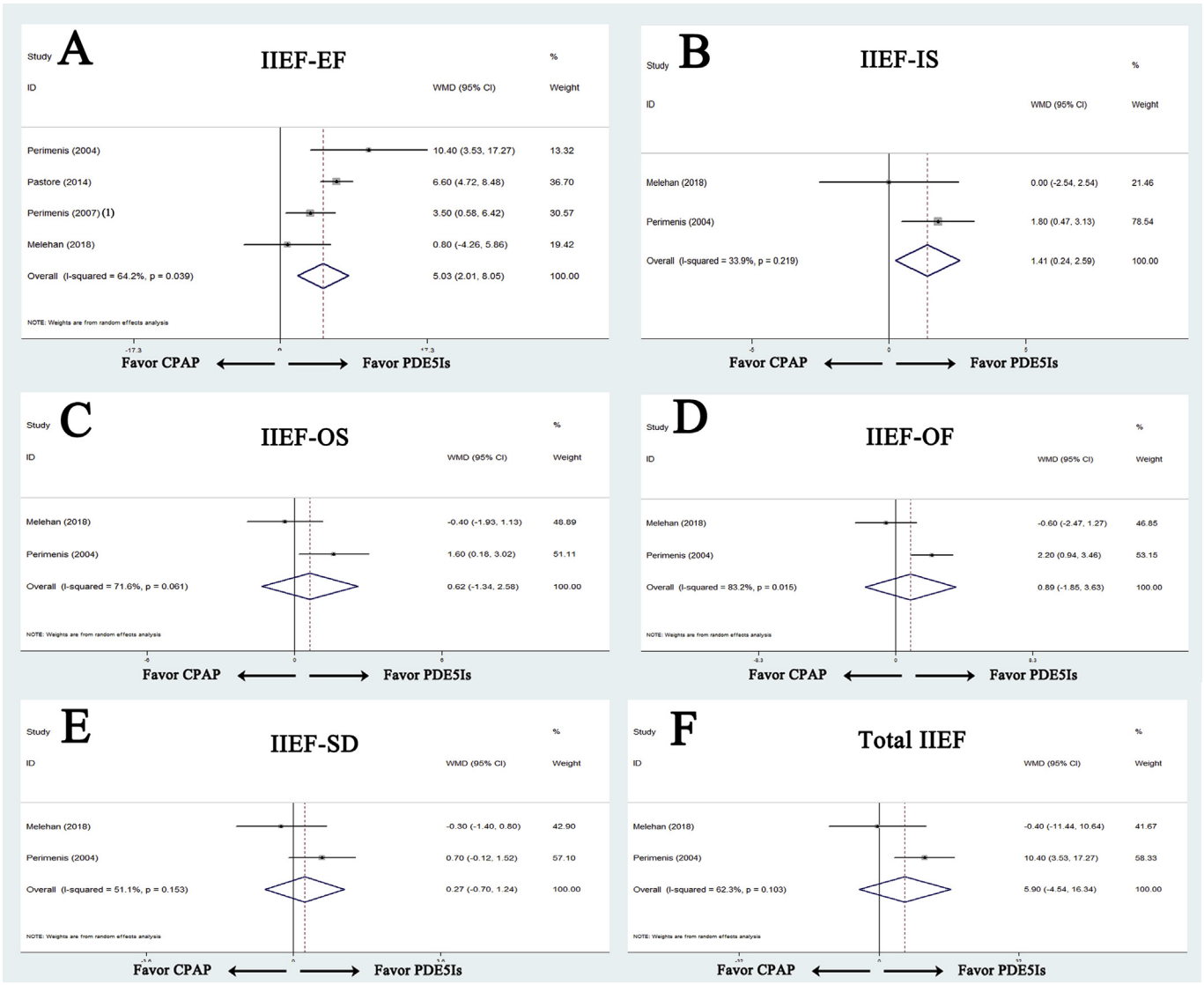

Fig. 3. Efficacy of CPAP versus PDE5i on IIEF score in men with OSA and ED. CI = confidence interval; CPAP = continuous positive airway pressure; ED: erectile dysfunction; IIEF = international index of erectile function; IIEF-EF = international index of erectile function-erectile function; IIEF-IS = international index of erectile function-intercourse satisfaction; IIEF-OF = international index of erectile function-orgasmic function; IIEF-OS = international index of erectile function-overall satisfaction; IIEF-SD = international index of erectile function-sexual desire; NPR = nocturnal penile rigidity; NPTC = nocturnal penile tumescence circumference; OSA = obstructive sleep apnea; PDE5i = phosphodiesterase type 5 inhibitors; WMD = weighted mean difference.

men. No evidence was found regarding the investigation about the efficacy of PDE5i versus PDE5i combined with CPAP on erectile function.

Sensitivity analysis and publication bias

We performed sensitivity analysis to assess the influence of individual trial on the pooled results. Results showed that significant differences were not introduced after omitting any of the included studies (Figure S3–S6). As for the pooled results for the effect of CPAP on IIEF-5 and efficacy of CPAP versus PDE5i on IIEF-EF, subgroup analysis stratified by severity of OSA, severity of ED, concurrent disease, administration pattern for PDE5i, sample size was performed. Results showed that any subgroup analysis could not interpret the source of heterogeneity (Table S7 and S8). Besides, no significant publication bias was found according to Egger's tests, indicating the robustness of the pooled results. The graphs of Egger's test were shown in Figure S7–S10.

Discussion

We performed the present systematic review to assess the effect of CPAP and PDE5i on erectile function in men with OSA and ED. The results revealed that CPAP significantly improved the IIEF score, TEE and NPR in OSA patients concurrent ED, whereas had no significant effect on NPTC. Moreover, CPAP was less effective than PDE5i in the treatment for ED, as indicated by lower IIEF-EF score, IIEF-IS score, EDITS-Q1 score, SAIR, and NPTC, whereas CPAP was more effective in TEE and of equal efficacy with PDE5i in the other domains of IIEF and NPR. Most outcome measures were evaluated as 'Low' or 'Very low' in GRADE assessment. Furthermore, PDE5i combined with CPAP seemed to ameliorate IIEF score, SAIR and TEE compared to CPAP alone, suggesting the superior efficacy of combined treatment.

Accumulated studies have demonstrated the close relationship between OSA and ED, with up to 80% prevalence of ED in OSA patients matched for age and comorbidities [6,7,40]. Given this

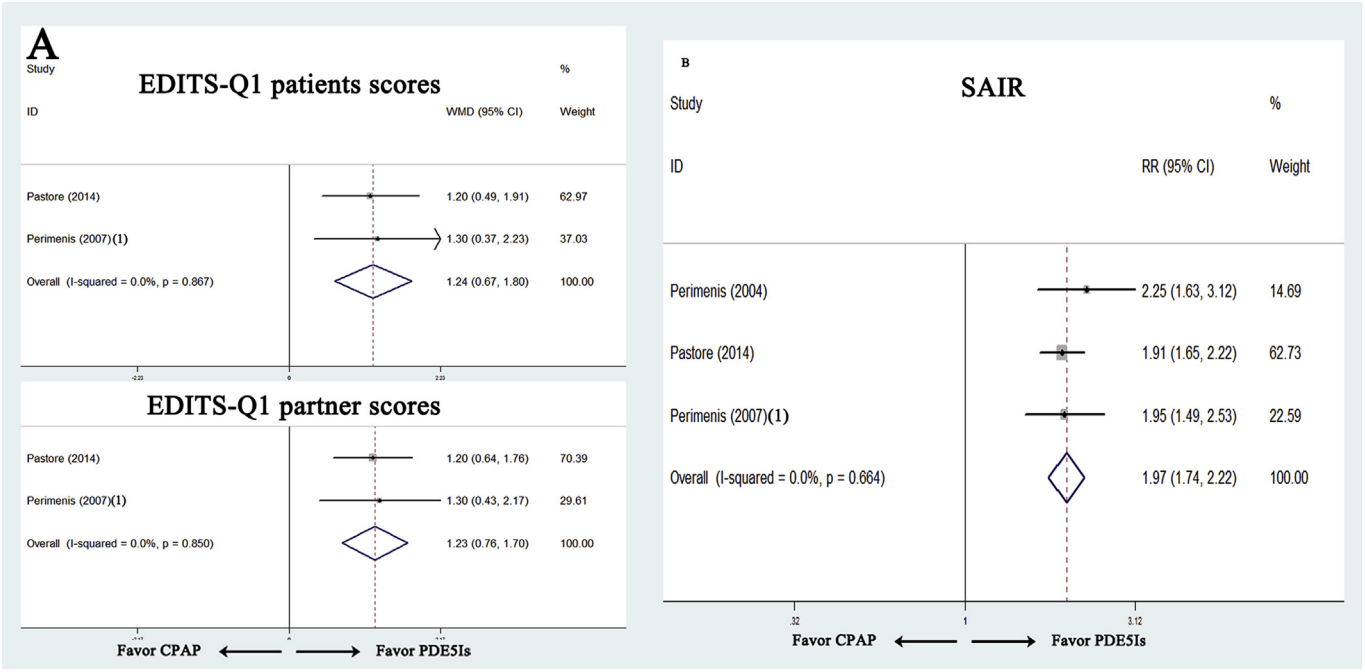

Fig. 4. Efficacy of CPAP versus PDE5i on EDITS-Q1 score and SAIR in patients with OSA and ED. CI = confidence interval; CPAP = continuous positive airway pressure; ED = erectile dysfunction; erectile dysfunction inventory of treatment satisfaction-question one = EDITS-Q1; OSA = obstructive sleep apnea; PDE5i = phosphodiesterase type 5 inhibitors; RR = relative risk; SAIR = successfull attempted intercourses rate; WMD = weighted mean difference.

growing evidence, some studies recommended to inquiry the snoring or sleep disturbances during ED assessment [41–43] and OSA was well recognized as the independent risk factor of ED [44]. In this context, many physiological hypotheses have been proposed regarding the link between OSA and ED. Hormonal, vasculogenic, neurogenic and psychogenic mechanisms are implicated in the pathogenesis of OSA-related ED. Some studies proposed that sleep disruption may interfere with the pituitary-gonadal axis and decrease the release of testosterone, which in turn damaged the libido [45,46]. Besides, nocturnal erections occur during rapid eye movement (REM) sleep [42], many researchers stated that OSA-related sleep fragmentation could disturb the REM sleep leading to the impairment of erectile function [47,48]. In terms of vasculogenic mechanism, hypoxic episodes could decrease the level of nitric oxide meanwhile stimulate endothelin production, and therefore impair the vascular endothelial function, which is regarded as the basis of neurovascular ED [49,50]. As for the neurogenic mechanism, Fanfulla et al. and Somers et al. found that peripheral nerve dysfunction and high sympathetic tone induced by OSA may undermine the erectile dysfunction [51,52]. Moreover, many psychogenic factors including daytime sleepiness, vigilance impairments, depressed mood caused by OSA could also decrease the libido [53–55]. Thus, identification of the pathogenesis of OSA-related ED may conduce to the individual therapeutic choice.

CPAP, as the standard therapy for OSA, its effect on erectile function remains controversial. Our pooled results indicated that CPAP significantly improved the IIEF score both in observational studies and RCT studies. As for the long-term effect of CPAP on erectile function, CPAP also tended to ameliorate IIEF score. IIEF questionnaire, as the golden standard for ED assessment, serves as a subjective outcome. Thus, we also investigated nocturnal penile tumescence (NPT), an objective indicator of organic impotence. Results showed that CPAP obviously improved TEE, NPR and NPTC, despite without reaching statistical significance in NPTC. Interestingly, IIEF score at baseline was inversely correlated with the improvements in erectile function after CPAP treatment, indicating that the beneficial effect of CPAP may be greater on OSA patients with higher severity of ED. Furthermore, we summarized the possible anti-ED mechanism of CPAP in included studies. Karacan et al. [29] and Melehan et al. [5] both reported that CPAP showed no significant effect on REM sleep patterns, indicating that REM disruption may not be a determining factor. Six trials attempted to investigate the role of testosterone on the anti-ED effect of CPAP [5,11,13,25,30,35]. However, CPAP seemed to not elevate the testosterone level (pooled WMD: 1.61, 95% CI: −1.39–4.60), which was consistent with a meta-analysis proposed at 2014 [56]. In addition, Melehan et al. assessed the endothelial function after CPAP treatment by flow-mediated dilatation or arterial tonometry [5]. Result showed that CPAP did not significantly improve endothelial function as well. Given the systemic effect of OSA, the mechanism of anti-ED effect of CPAP might be multifactorial and further researches are therefore expected.

To date, the efficacy of CPAP versus PDE5i on erectile function in men with OSA and ED remains unclear. Pooled results showed that CPAP was inferior to PDE5i in improving IIEF-EF, IIEF-IS score, and SAIR. However, they were of equal efficacy in improving IIEF-OS, IIEF-OF, IIEF-SD, and total IIEF score. IIEF questionnaire, as a self-reported outcome, is predisposed to the placebo effect. Consequently, we summarized the data of a randomized sham-controlled trial [5]. Results showed that PDE5i tended to be more effective than CPAP in improving IIEF-EF score, while no significant differences were observed in all the domains of IIEF, which indicated that the placebo effect should be fully considered in further studies of ED treatment. Notably, it seemed that PDE5i was superior to CPAP in erectile function domain rather than other IIEF domains. It was possibly attributed to the different mode of action between two treatments. CPAP acts in a systemic way. In contrast, PDE5i takes effect in the peripheral organ, which directly restores the erectile response by relaxing smooth muscle in the penile erectile tissue [57]. In our review, one placebo-based trial reported NPT [5].

Interestingly, CPAP was more effective than PDE5i in improving TEE, despite a lower efficacy in NPTC. Nocturnal erections, regarded as a factor in maintaining erectile function [29,58,59], its improvements might precede any daytime alteration of erectile function. Thus, we speculated the effect of CPAP on nocturnal erections may be more direct and essential than its daytime effect.

The satisfaction with treatment greatly influences the compliance of patients, which further determines the efficacy of treatment. Therefore, we summarized the available evidence about the satisfaction with CPAP and PDE5i among patients with OSA and ED. Pooled results showed that EDITS-Q1 patient and partner score were significantly higher in PDE5i group than that in CPAP group, and it must be noted that poor adherence to CPAP might weaken its inherent anti-ED effect. Besides, the original EDITS-Q1 scores of two groups were both relative lower than expected, and hence their combination therapy or other therapeutic methods should be further explored.

Hitherto, several RCTs have investigated the effect of PDE5i combined with CPAP on erectile function in men with OSA and ED. However, the studies remain rare but promising. Based on our search profile, three trials were identified. We found that compared to PDE5i alone, the combination of CPAP and PDE5i tended to ameliorate IIEF score, SAIR, and TEE. According to the data from Perimenis et al. [4], overall satisfaction with the combination therapy reached to 70%, indicating that combination therapy with CPAP and PDE5i was well tolerated and may be a promising therapeutic alternative for OSA patients concurrent ED. However, given the small sample size, the strength of the current evidence was inadequate and far from persuasive. Therefore, further studies investigating the efficacy of combination therapy remain to be implemented.

Applying the GRADE approach, We further judged the quality of evidence of the pooled outcomes. The majority of outcomes were graded as 'Low' or 'Very low' except the outcome of SAIR as 'Moderate'. According to the current evidence, CPAP could significantly improve erectile dysfunction in OSA patients. Besides, PDE5i was superior to CPAP in improving erectile function. Thus, clinicians should be more prone to recommend PDE5i or combined treatment as the therapy for patients with OSA and ED. However, the quality of evidence and its recommended strength was low. More high-quality RCT studies are therefore expected to further validate these findings.

Several limitations of the current review should be acknowledged. Firstly, the majority of included studies did not have adequate blinding which made them prone to potential bias. However, blinded trials were difficult to be conducted on account of the distinctive nature of the two interventional modalities. Secondly, we were unable to strictly correct the comorbidities that may affect ED. According to the study of Daskalopoulou-Vlahogianni et al. [37], comorbidities like diabetes and hypertension may serve as prognostic factors for the improvement of erectile function caused by CPAP. Thus, ED-related comorbidities may influence the patients' response to the treatment, which may introduce some bias to the result. Thirdly, only about half of the studies clearly reported the effect of CPAP on OSA, which may lead to the masking of its therapeutic effect on ED due to its ineffective CPAP intervention. Fourthly, the majority of studies had focused on short-term outcomes. Given the chronic progressive feature of OSA and ED, the long-term effect of CPAP on erectile function remained to be fully elucidated.

Conclusions

CPAP significantly improved not only the subjective outcome of IIEF score but also the objective indicator of TEE and NPR in men with OSA and ED, while no significant changes of NPTC. Besides, CPAP was inferior to PDE5i in improving IIEF-EF, IIEF-IS, EDITS-Q1 score, SAIR, and NPTC, whereas was more effective in TEE and of equal efficacy with PDE5i in other domains of IIEF and NPR. Furthermore, compared to CPAP alone, the combination of CPAP and PDE5i tended to ameliorate IIEF score, SAIR, and TEE with good tolerance. However, the strength of current evidence regarding the combination therapy was inadequate. Therefore, further studies remain to be implemented.

Practice points

1. CPAP significantly improved IIEF score, TEE and NPR in men with OSA and ED.
2. The beneficial effect of CPAP may be greater on OSA patients with higher severity of ED.
3. CPAP was less effective than PDE5i in IIEF-EF, IIEF-IS, EDITS-Q1 score, NPTC, and SAIR, while more effective than PDE5i in TEE.
4. The placebo effect should be a concern in the clinical trials investigating the treatment of ED.
5. Combination therapy with CPAP and PDE5i seemed to be superior to CPAP alone in improving erectile function, which may be a promising therapeutic alternative for OSA patients concurrent ED.

Research agenda

1. Future researches should focus on the underlying mechanism of anti-ED effect of CPAP.
2. Randomized sham-controlled blinded trial should be performed to compare the efficacy between CPAP, PDE5i and combination therapy on the erectile function in men with OSA and ED.
3. The long-term effect of CPAP on erectile function remained to be fully elucidated.
4. ED-related comorbidities may influence the patients' response to the treatment. Further clinical studies should fully assess these comorbidities during the phrase of recruitment.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.101217.

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