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Meta-Analysis of Efficacy and Safety of Tadalafil Plus Tamsulosin Compared with Tadalafil Alone in Treating Men with Benign Prostatic Hyperplasia and Erectile Dysfunction

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Abstract

This meta-analysis was performed to evaluate the efficacy and safety of tadalafil plus tamsulosin compared with tadalafil alone in treating men with benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) after 12 weeks' treatment. Systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analyses. MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched to collect randomized controlled trials. The references of related articles were also searched. Four articles including 621 patients were involved in the analysis. The study identified that combination-therapy had significant improvements in total international prostate symptom score (IPSS), quality of life (QoL) and maximum urine flow rate (Qmax) compared with monotherapy, and there were no obvious significance in respects of post-void residual volume, international index of erectile function and IPSS storage. The difference of total IPSS was mainly reflected in the change of IPSS voiding. For safety, combination-therapy had a higher incidence rate of any adverse events (AEs) and discontinuation due to AEs than monotherapy with the exception of pain. In conclusion, the combination of tadalafil and tamsulosin provided a better improvement of IPSS voiding, QoL and Qmax compared with tadalafil alone in treating men with BPH and ED, and the former therapy appeared to show a higher incidence of AEs.

Keywords

benign prostatic hyperplasia, erectile dysfunction, tadalafil, tamsulosin, meta-analysis

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Benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) are common geriatric diseases and their occurrence rate increases with the growth of age (Emberton et al., 2003; Nicolosi, Moreira, Shirai, Bin Mohd Tambi, & Glasser, 2003). Male patients with BPH not only suffer frequently from lower urinary tract symptoms (LUTS) (mainly including urination at night, interrupted urine flow, sense of incomplete bladder voiding and high-risk of acute urinary retention, etc) but also from ED and ejaculatory dysfunction, which have a greater unpleasant impacts on the patient's life (Anderson, Roehrborn, Schalken, & Emberton, 2001; Rosen, 2006; Vallancien, Emberton, Harving, & van Moorselaar, 2003).

Tadalafil, a long-lasting phosphodiesterase type 5 (PDE5) inhibitor, has globally been approved to treat ED

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and meanwhile relieve related symptoms of BPH (Andersson et al., 2011; Chapple et al., 2015). Although tadalafil monotherapy shows a powerful effect in treating male ED with LUTS, the role of combination-therapy is less understood in clinical. Tamsulosin, as an alpha-blocker approved to treat LUTS, has a significant effect on improving subjective symptoms of patients, and the correlation between the drug and ED has been studied in clinical trials (Hofner, Claes, De Reijke, Folkestad, & Speakman, 1999; Zhang et al., 2017). However, there were few evidence-based medicine studies focusing on the combination-therapy of two drugs. Given that tadalafil and tamsulosin have different mode of action, the combination-therapy of two drugs have become an alternative treatment mode for men with BPH and ED.

The meta-analysis was conducted to evaluate the efficacy and safety of the combination of tadalafil and tamsulosin compared with tadalafil alone in treating men with BPH and ED after 12 weeks' treatment.

Materials and Methods

Study Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to systematic review of randomized controlled trials (RCTs) (Moher, Liberati, Tetzlaff, & Altman, 2009).

Information Sources and Literature Search

Based on sources including MEDLINE (1996 to Jul 2018), EMBASE (1999 to Jul 2018) and the Cochrane Controlled Trials Register, reviewers did a comprehensive search to investigate the combination of tadalafil and tamsulosin versus tadalafil alone in treating men with BPH and ED after 12 weeks' treatment. The search terms was as follows: "tadalafil, tamsulosin, ED and BPH." Two reviewers browsed all articles independently, and when there was any controversy, articles would be sent to the third author for assessment. The analysis only included published articles with no restriction on language or region. If the study was a review or summary presented at the meeting, it would be excluded. If necessary, authors would be contacted to provide more accurate data from their researches. The references of related articles were also searched.

Inclusion Criteria and Trial Selection

Inclusion criteria was as follows: (1) The combination of tadalafil and tamsulosin versus tadalafil alone in treating BPH and ED was involved; (2) Full-text content and related data can be obtained; (3) Articles offered accurate data mainly including the number of subjects and the valuable results of indicators; (4) Trials were randomized controlled study; (5) The duration of medication was 12 weeks. If a study was published by several magazines, the latest findings would be added to our study. Each study was added to this article if a group of patients took part in multiple studies. The PRISMA diagram of selection is presented in Figure 1.

Quality Assessment Methods

The Jadad Scale was used to evaluate the quality of each RCT (AR, 1998). Additionally, some methods of assessment were used to analyze the quality of the individual studies, including method of patient allocation, concealment of allocation, blinding method and number of lost to follow-up. Individual study was graded in line with the principles which derived from the *Cochrane Handbook for Systematic Reviews of Interventions v5.10* (Higgins JP). Every study was classified based on quality assessment criteria: (A) Satisfying almost all of the quality criteria, study would be considered to have a low probability of bias; (B) Satisfying the partial quality criteria or unclear, the study was thought of having a secondary probability of bias; or (C) Satisfying bare quality criteria, the study was considered to have a high probability of bias. All authors participated in the assessment of retrieved studies, eventually everyone agreed with this results. All reviewers independently assessed whether the study fitted into the criteria, and then extracted data from studies. Differences regarding the quality assessment were resolved by discussion among the reviewers.

Data Extraction

The information extracted from included studies was: (A) Published time; (B) The first author' name; (C) Country of study; (D) The type of design; (E) Patient's received therapy; (D) Number of participants in each group; (E) Drug management; (F) Treatment period; (G) Drug dose; (H) Data on total international prostate symptom score (IPSS), quality of life (QoL), IPSS storage, IPSS voiding, maximum urine flow rate (Qmax), post-void residual volume (PVRV), international index of erectile function (IIEF), any adverse events (AEs), discontinuation due to AEs and pain (including headache, myalgia, back pain and bone pain). Because they have a measurable impact on patient, these results were considered as meaningful indicators. No ethical approval was required for the study.

The primary outcome was IPSS. The higher scores of IPSS indicated a more severe symptoms. And secondary outcomes including QoL, Qmax, IIEF and PVRV, these were reported consistently enough among studies to allow for analysis of data. In addition, the study analyzed the

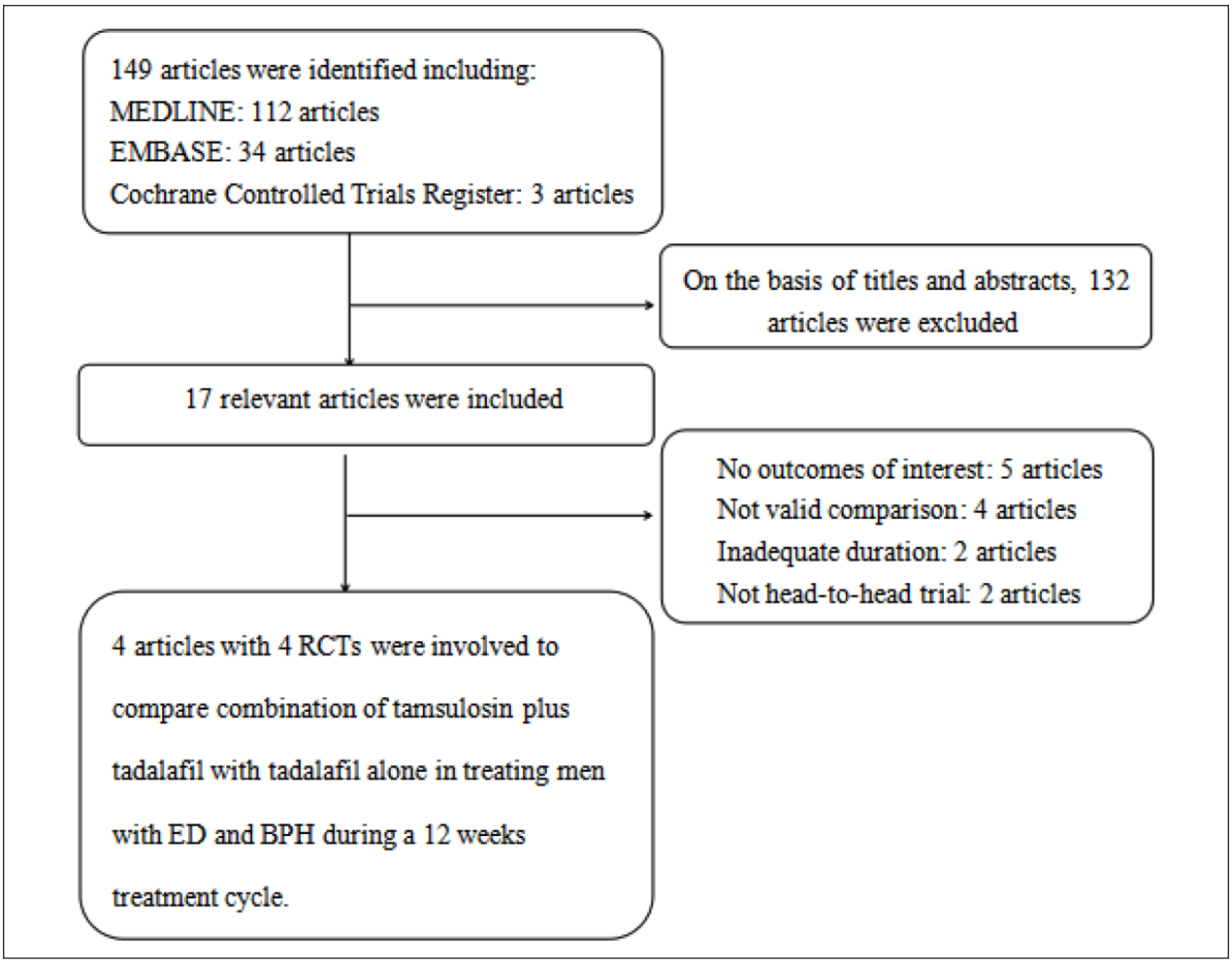

Figure 1. Flowchart of the study selection process. RCT, randomized controlled trials; BPH, benign prostatic hyperplasia; ED, erectile dysfunction.

number of any AEs, discontinuation due to AEs and pain (including headache, myalgia, back pain and bone pain).

Statistical Analyses and Meta-Analysis

Rev Man version 5.3.0 (Cochrane Collaboration, Oxford, UK) (AR, 1998) was used to the analysis of data. Fixed or random effects models were applied to assess the study. Mean difference (MD) was used to explain continuous data and odds ratio (OR) for dichotomous results with the corresponding 95% confidence interval (CI). If analysis showed p-value $>.05$, the study was homogeneous, and fixed-effect model was used in the study. The study analyzed inconsistency by using I^2 statistic that reflected the proportion of heterogeneity in data analysis. A random effect model would be used for results where the I^2 value is greater than 50% and has significant heterogeneity. If p-value was less than .05, the result was considered to have statistically significant.

Results

Study Selection Process, Search Results, and Characteristics of the Trials

The search found 149 articles in database. Scrutinizing all abstracts and titles, reviewers excluded 132 articles. For remaining 17 articles, 13 articles were excluded because of lacking of available data (details in Figure 1). Finally, 4 articles containing 4 RCTs (Dell'Atti & Cuneo, 2013; Karami, Hassanzadeh-Hadad, & Fallah-Karkan, 2016; Kim et al., 2017; Singh, Mete, Mandal, & Singh, 2014) were used to evaluate combination of tadalafil and tamsulosin compared with tadalafil alone in treating men with BPH and ED after 12 weeks' treatment. The details of four articles were listed in Table 1. Patients with ED and BPH included in each study showed similar evaluation index. The baseline characteristics of patients were listed in Table 2.

Table 1. The Details of Individual Study.

Study	Country	Study design	Therapy in experimental group	Therapy in control group	Sample size		Method	Time of therapy (weeks)	Dosage (mg/mg)	Main inclusion criteria	Outcome measures
					Experimental	Control					
Dell'Atti and Cuneo (2013)	Italy	RCT	Tamsulosin plus tadalafil	Tadalafil	49	51	Oral	12	0.4 mg+5 mg/5 mg	Men ≥50 years of age with a history of ED and BPH, IPSS ≥8, PSA ≤2.5 ng/ml, Qmax >5 ml/s and <15 ml/s, PVR<120 ml, IIEF ≥11, PV ≤40 ml.	Toal IPSS, QoL, Qmax, PVR, IIEF-5
Singh et al. (2014)	India	RCT	Tamsulosin plus tadalafil	Tadalafil	44	44	Oral	12	0.4 mg+10 mg/10 mg	Men ≥45 years of age with a history of LUTS secondary to BPH of 6 months or longer, IPSS >8, PSA ≤4.0 ng/ml, Qmax >5 ml/s and <15 ml/s, MVV >125 ml.	Toal IPSS, QoL, Qmax, PVR, IIEF-5
Karami et al. (2016)	Iran	RCT	Tamsulosin plus tadalafil	Tadalafil	58	60	Oral	12	0.4 mg+20 mg/20 mg	Men older than 45 years old, IPSS ≥ 12, and having a history of ED.	Toal IPSS, Qmax, PVR, IIEF-5, IPSS storage, IPSS voiding
Kim et al. (2017)	Korea	RCT	Tamsulosin plus tadalafil	Tadalafil	153	162	Oral	12	0.4 mg+5 mg/5 mg	Men older than 50 years with BPH (total IPSS ≥13), ED for at least 3 months, Qmax of 4 to 15 ml/s, MVV ≥125 ml, PVR >300 ml, IIEF ≤25.	Toal IPSS, QoL, Qmax, PVR, IIEF-5, IPSS storage, IPSS voiding

Note. BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; Qmax, maximum urine flow rate; PSA, prostate specific antigen; PV, prostate volume; PVR, post-void residual; LUTS, lower urinary tract symptoms; ED, erectile dysfunction; IIEF; International Index of Erectile Function; MVV, minimum voided volume, RCT, randomized controlled trial; QoL, quality of life.

Table 2. The Baseline Characteristics of Individual Study.

Study	Group	Age (years)	BMI (kg/m^2)	QoL	IIEF-5	PV (ml)	PSA (ng/ml)	IPSS			Qmax (ml/s)	PVR (ml)
								Total IPSS	IPSS storage	IPSS voiding		
Dell'Atti and Cuneo (2013)	Combination	63.4 ± 10.33	-	2.56 ± 0.88	13.40 ± 4.20	40.30 ± 11.19	1.60 ± 0.80	13.66 ± 4.35	-	-	9.09 ± 2.91	26.87 ± 22.95
	Tadalafil	63.80 ± 10.15	-	2.19 ± 0.67	12.90 ± 3.10	42.00 ± 11.18	1.50 ± 0.70	13.06 ± 4.38	-	-	8.9 ± 2.96	26.06 ± 24.33
Singh et al. (2014)	Combination	61.92 ± 6.29	-	5.65 ± 0.56	10.61 ± 5.58	-	≤4.00	21.73 ± 5.88	-	-	9.88 ± 3.58	126.31 ± 78.51
	Tadalafil	63.42 ± 8.09	-	5.75 ± 0.44	11.77 ± 6.38	-	≤4.00	20.33 ± 5.66	-	-	8.83 ± 3.54	98.92 ± 84.50
Karami et al. (2016)	Combination	67.90 ± 8.80	27.10 ± 2.30	4.10±1.20	10.60 ± 1.70	63.20 ± 12.10	2.1±1.6	21.20 ± 7.50	6.60 ± 3.20	14.60 ± 4.00	12.40 ± 4.80	58.60 ± 60.20
	Tadalafil	68.2 ± 7.80	27.40 ± 1.20	3.90±1.30	10.10 ± 1.80	59.60 ± 14.10	2.5±1.8	19.90 ± 6.30	5.80 ± 2.10	14.90 ± 4.10	12.60 ± 5.40	61.60 ± 63.30
Kim et al. (2017)	Combination	61.84 ± 5.71	24.83 ± 2.68	4.21 ± 0.77	14.19 ± 5.20	-	-	21.36 ± 5.55	7.83 ±2.76	13.53 ±3.50	10.75 ± 2.46	36.19 ± 43.78
	Tadalafil	61.93 ± 6.83	24.60 ± 2.41	4.08 ± 0.79	14.57 ± 5.04	-	-	20.12 ± 5.44	7.34 ± 2.66	12.78 ± 3.88	10.28 ± 2.47	35.85 ± 45.95
Mean±SD		64.05 ± 2.42	25.98 ± 1.27	4.06 ±1.18	12.27 ± 1.63	51.28 ±10.22	1.93 ± 0.40	18.92 ±3.27	6.89 ± 0.77	13.95 ±0.85	10.34 ±1.39	58.8 ± 34.10

Note. Data presented as mean ± SD. SD, standard deviation; IPSS, International Prostate Symptom Score; Qmax, maximum urine flow rate; PSA, prostate specific antigen; PV, prostate volume; PVR, post-void residual; BMI, body mass index; QoL, quality of life; IIEF, International Index of Erectile Function.

Table 3. Quality Assessment of Individual Study.

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Level of quality	ITT analysis
Dell'Atti and Cuneo (2013)	A	A	A	4	Yes	T-tests; Chi-square test; ANOVA	A	No
Singh et al. (2014)	A	A	A	1	Yes	T-tests; ANOVA	A	No
Karami et al. (2016)	A	A	A	0	Yes	T-tests; Fisher's exact test; ANOVA	A	No
Kim et al. (2017)	A	A	A	10	Yes	ANOVA; Chi-square test; Fisher's exact test	A	Yes

A, almost all quality criteria met: low risk of bias; B, one or more quality criteria met: moderate risk of bias; C, one or more criteria not met: high risk of bias; ITT, intention-to-treat; ANOVA; analysis of variance.

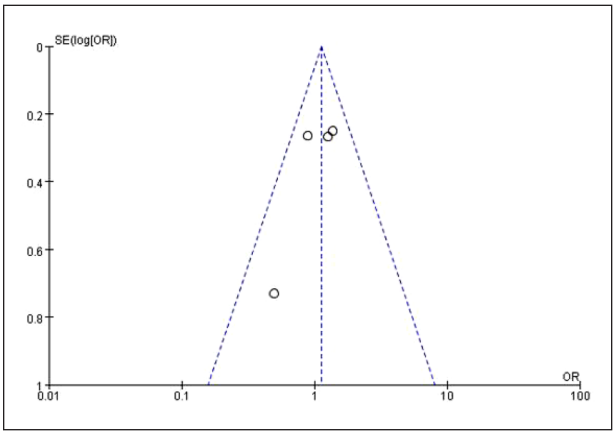

Figure 2. Funnel plot of the studies included in the meta-analysis. OR, odds ratio; SE, standard error.

Risk of Bias in Studies

All studies included in the analysis were random control study and did a specified random protocol. Four studies had an appropriate calculation of sample size to analyze. Only one study (Kim et al., 2017) reported intention-to-treat analysis. The specific methods of blind were explicitly explained with their Jadad scores rating A (Table 3). Besides, the difference in tadalafil doses may also lead to bias of results. The plot was highly symmetrical and four squares were contained in the large triangle, and no evidence of bias was identified (Figure 2). Risk of bias summary and graph has presented in Figure 3.

Efficacy

Total IPSS, IPSS Storage and IPSS Voiding. Four RCTs with a total of 621 patients (304 in the combination group and 317 in the tadalafil group) were used to analyze the change of total IPSS. The forest plot demonstrated that the combination group had a greater decrease of total IPSS (MD −3.21, 95% CI −4.88 to −1.55, $p = .0001$) (Figure 4A) compared with the tadalafil group. This result suggested that combination of tadalafil and tamsulosin can significantly alleviate the subjective symptoms of patients.

In terms of IPSS storage and IPSS voiding, two RCTs had an appropriate sample size of 433 patients (211 in the combination group and 222 in the tadalafil group). For IPSS storage, the random-effects estimate of MD was −0.75, and the 95% CI was −1.59 to 0.10 ($p = .08$) (Figure 5A). For IPSS voiding, the fixed-effects estimate of MD was −1.00, and the 95% CI was −1.06 to −0.94 ($p < .00001$) (Figure 5B). This result indicated that the difference of total IPSS might be represented primarily in the change of IPSS voiding.

QoL. Three RCTs with an amount of 503 patients (246 in the combination group and 257 in the tadalafil group) included data on the change of QoL. The combination group was significantly superior to the tamsulosin group in reducing QoL (MD −0.36, 95%CI −0.62 to −0.10, $p = .007$) (Figure 4B). This result suggested that combination of tadalafil and tamsulosin can significantly improve the quality of life of patients compared with tadalafil monotherapy.

Qmax. Four RCTs with a amount of 621 patients (304 in the combination group and 317 in the tadalafil group) contained data on the Qmax. The forest plots showed a MD of 0.98 and 95% CI of 0.86 to 1.10 ($p < .00001$) (Figure 6A). This result identified that combination of tadalafil and tamsulosin had a significant improvement in terms of Qmax compared with tadalafil monotherapy.

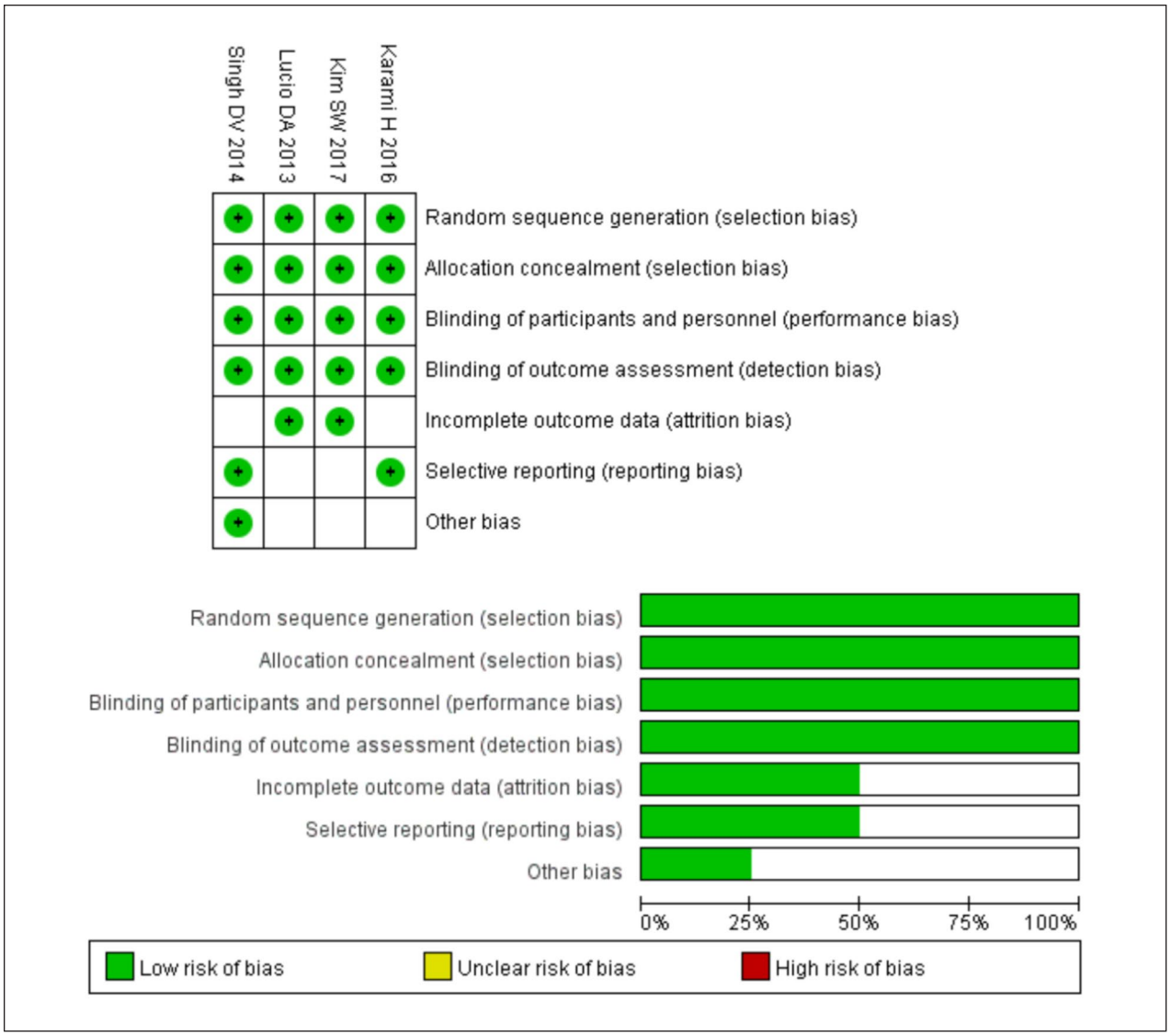

Figure 3. Risk of bias summary and graph.

PVRV and IIEF. Four RCTs included data on the PVRV and IIEF, with an amount of 621 patients (304 in the combination group and 317 in the tadalafil group). The model showed no marked differences between the combination group and the tadalafil group in the change of PVRV (MD −9.02, 95%CI −21.82 to 3.79, $p = .17$) (Figure 6B) and IIEF (MD 0.10, 95%CI −0.63 to 0.84, $p = .79$) (Figure 6C).

Safety

Any AEs. Four RCTs with a sample of 621 patients (304 in the combination group and 317 in the tadalafil group) evaluated the incidence of AE. The study showed a significant difference between combination group and tadalafil group in the incidence of all AE across four studies (OR 1.59, 95%CI 1.08 to 2.36, $p = .02$) (Figure 7A).

Discontinuation due to AEs. Four RCTs accessed the incidence of discontinuation due to AEs with a sample size of 621 patients (304 in the combination group and 317 in the tadalafil group). The OR was 1.70 and 95% CI was 1.02 to 2.86 ($p = .04$) (Figure 7B). This result suggested that the combination group showed the higher incidence in discontinuation due to AEs.

Pain (including headache, myalgia, back pain and bone pain). Four RCTs with a sample of 621 patients (304 in the combination group and 317 in the tadalafil group) analyzed the severity of pain after taking medicine. A

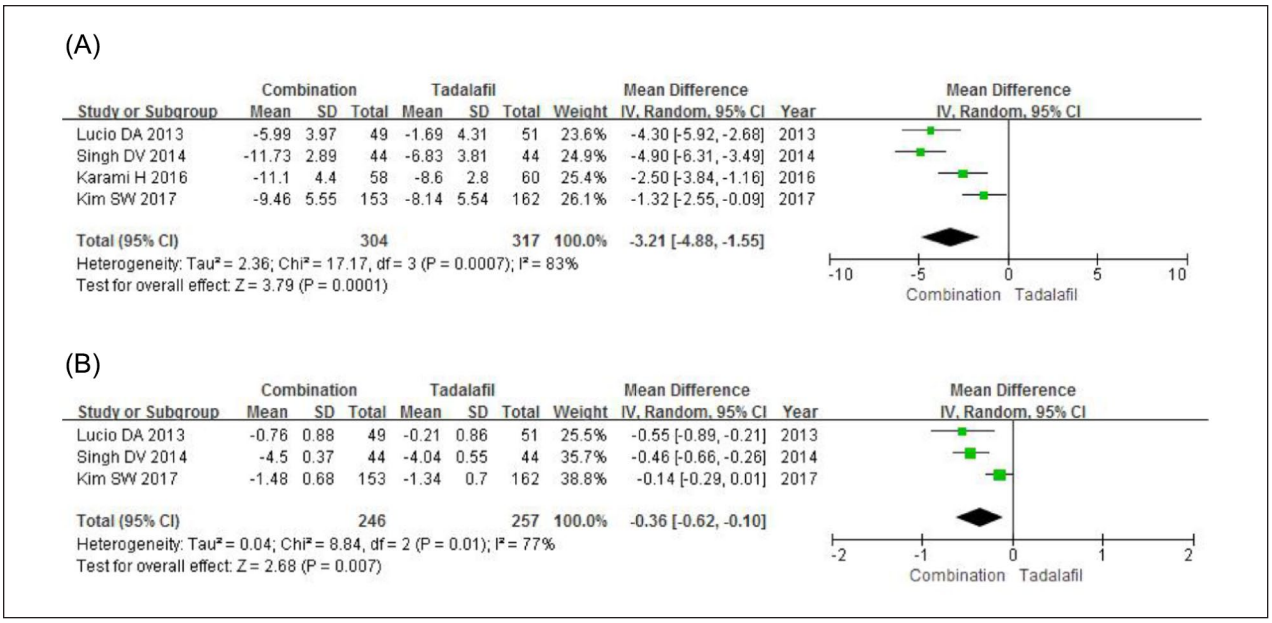

Figure 4. Forest plots showing changes in (A) total IPSS; (B) quality of life; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

fixed-effects model showed no statistical significance between the combination group and tadalafil group in the occurrence rate of pain associated with medication (OR 1.50, 95%CI 0.86 to 2.64, $p = .16$) (Figure 7C).

Discussion

ED and LUTS are closely related with some unpleasant symptoms and poorer quality of life for elderly male (Coyne et al., 2009; Platz et al., 2012). As the prevalence of ED and LUTS increases with age, physicians should be in the position to manage these two conditions simultaneously (El-Sakka, 2006). In many cases, alpha blockers are considered the most effective monotherapy for LUTS suggestive of BPH, meanwhile PDE5 inhibitors are the first-line treatment for ED ("AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations," 2003; Porst et al.,

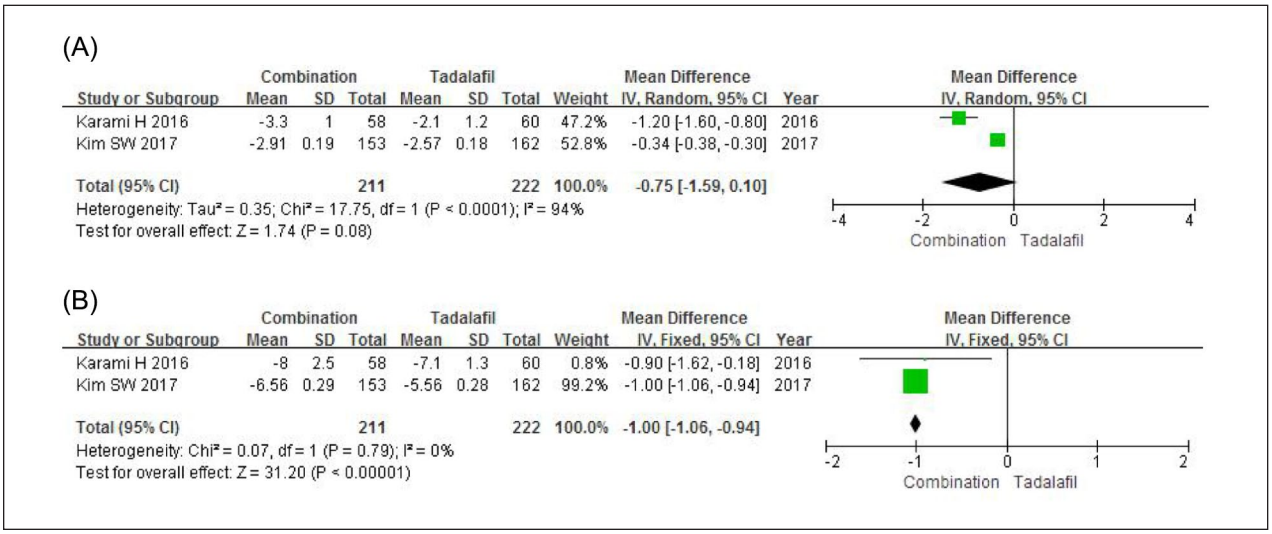

Figure 5. Forest plots showing changes in (A) IPSS storage; (B) IPSS voiding; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

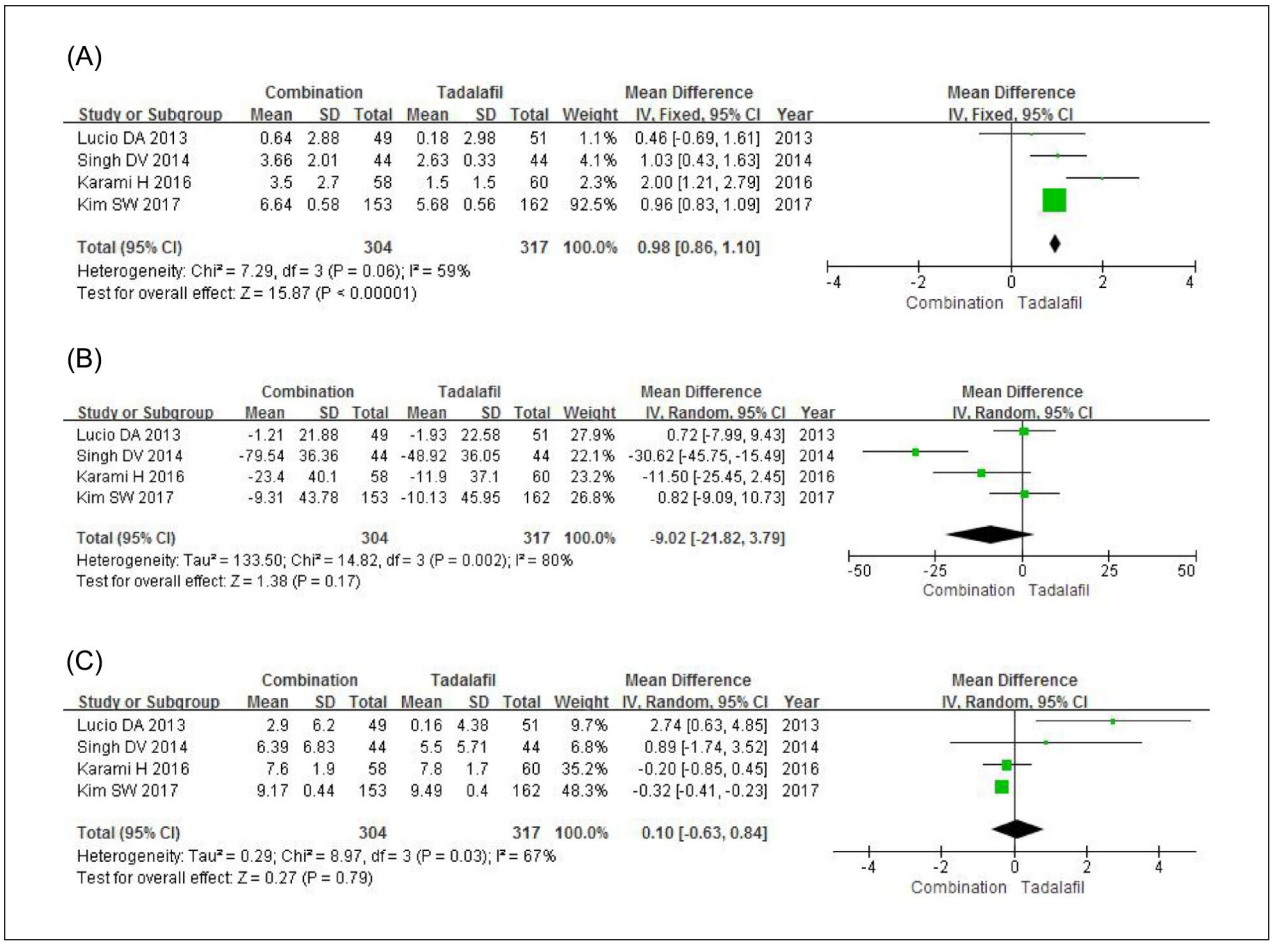

Figure 6. Forest plots showing numbers in (A) maximum urine flow rate; (B) post-void residual volume; (C) International index of erectile function; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

2013). The co-administration of alpha blockers and PDE5 inhibitors to treat BPH and ED showing strong similarities in their pathophysiology and comorbidity, has recently exhibited an increase in popularity (Bechara et al., 2008). Tamsulosin, approved by the Food and Drug Administration, is the only alpha blocker to be used in combination with tadalafil (Kloner, 2004). In addition, numerous researchers assessed the actions of PDE5 inhibitors in improving the symptoms of LUTS and in vitro and in vivo role of alpha blockers and PDE5 inhibitors for ED improvement (Yan, Zong, Cui, Li, & Zhang, 2014).

This meta-analysis was performed from four studies including 621 participants to compare the efficacy and safety of combination of tadalafil and tamsulosin compared with tadalafil alone in treating BPH and ED after 12 weeks of treatment. The study identified that the combination therapy had a greater decrease compared with tadalafil monotherapy in terms of total IPSS, IPSS voiding and QoL. Four RCTs containing data on Qmax showed a marked improvement in the combination therapy relative to the tadalafil group. But in terms of IPSS storage, PVRV and IIEF, there were no apparent differences among two therapeutic regimens.

This analysis suggested that the combination-therapy of tadalafil and tamsulosin was more effective than tadalafil alone in improving subjective LUTS, but there was no significant improvement in sexual function. Besides, the difference of total IPSS was mainly reflected in the change of IPSS voiding, which further proved that tamsulosin might improve the total IPSS through relieving symptoms during urination. Kim et al. (2017) demonstrated that the combination of tamsulosin and tadalafil (0.4 mg/5 mg) was determined to be safe, efficacious, and well tolerated in the subjects investigated, which suggested the fixed-dose regimen can offer clinically relevant benefits for patients with LUTS complaints and desiring amelioration for comorbid ED complaints.

The pharmacological action by which combination therapy produced greater improvements than monotherapy is not yet very clear. It was postulated that both

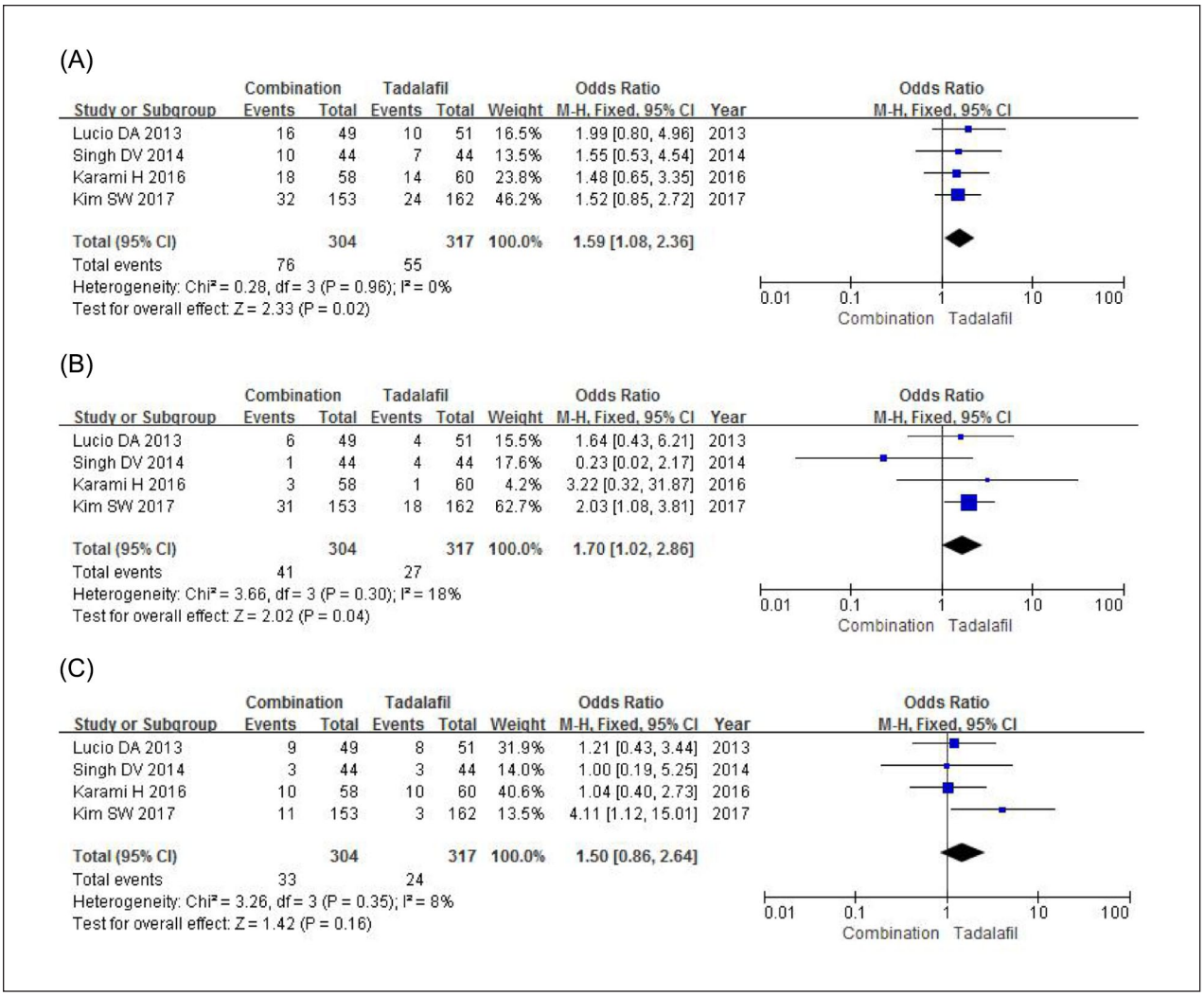

Figure 7. Forest plots showing numbers in (A) any adverse events; (B) discontinuation due to adverse events; (C) pain (including headache, myalgia, back pain and bone pain); M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

alpha-1 blockers and PDE5 inhibitors, acting by two different mechanisms of action on common urogenital target organs, may have a synergistic effect on LUTS and ED. Clinical studies have reported that alpha-1 blockers can enhance the NO mediated relaxant influence of PDE5 inhibitors by blocking alpha-1-adrenergic receptors and lowering the sympathetic tone in penile smooth muscle and prostate/bladder neck (Carson, 2006; Oger et al., 2008). Similarly, one study reported that PDE5 inhibitors strengthened the inhibiting actions of alpha-1 blockers on neurogenic contractions of prostate and bladder neck (Angulo et al., 2012). Dunn, Althof, and Perelman (2007) reported that prolonged duration of action of tadalafil is more suitable for alleviating some of the psychological barriers that interfere with treating ED and provides some men with ED and their partners a treatment option that may offer greater flexibility and potentially less anxiety surrounding the resumption of sexual activity.

The safety indexes included in the study suggested that both two groups were well tolerated. For some adverse reactions, such as any AEs and discontinuations due to AEs, the combination group showed a higher incidence compared with the tadalafil group. But one RCT (Karami et al., 2016) reported that the complications of combination therapy were myalgia, headache, back pain and nasopharyngitis dizziness. Although the complication rate was higher in combination therapy group compared to monotherapy group, it was not significant. Based on the our analysis, it is strongly recommended that physicians should explain to patients potential serious side effects of long-term combination of tadalafil and tamsulosin before adopting this treatment.

The combination of tadalafil and tamsulosin provides a better improvement of IPSS voiding, QoL and Qmax compared with tadalafil alone in treating men with BPH and ED after 12 weeks of treatment, and the former

appears to show a higher incidence of AEs. Furthermore, one sudy (Donatucci et al., 2011) found that 5 mg of tadalafil once daily was well tolerated after 1 year of treatment, which suggested that long-term treatment of tadalafil 5 mg once-daily in men with BPH-LUTS provided a favorable risk–benefit profile.

The reader must acknowledge the limitations of this meta-analysis. The quality of these studies is flawed, primarily in terms of study design, patient selection, blinding, and outcome data. The results of meta-analysis should be interpreted carefully. Those articles included in study were all randomized controlled trials to reinforce the findings.

This analysis could not infer the long-term efficacy and tolerance of combination therapy, and selection bias, subjective factors, publication bias and non-fixed dose regimen may also affect the final results of the study. Our findings should be confirmed with RCTs with long-term follow-up, sufficient sample size, and fixed-dose data. More high-quality RCTs with suitable study cohorts are needed to ascertain the efficacy and tolerance of combination of tadalafil and tamsulosin in treating men with BPH and ED.

Conclusions

The combination of tadalafil and tamsulosin provides a better improvement of IPSS voiding, QoL and Qmax compared with the tadalafil alone in treating men with BPH and ED after 12 weeks of treatment. But, combination of tadalafil and tamsulosin seems to have a higher incidence of AEs.

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