Systematic Review and Meta-Analysis

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Efficacy and tolerability of combination therapy with alpha-blockers and phosphodiesterase-5 inhibitors compared with monotherapy for lower urinary tract symptoms

Protocol for a systematic review and network meta-analysis

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Abstract

Purpose: This study aimed to compare the efficacy and safety of combination therapy consisting of α-blockers and different phosphodiesterase type 5 inhibitors for lower urinary tract symptoms (LUTS) by performing a network meta-analysis.

Method: Relevant articles were retrieved from the Cochrane Library, PubMed, and EMBASE databases. Bayesian network meta-analyses were performed with a random-effect model to compare the efficacy and safety of combination therapy with α-blockers and phosphodiesterase-5 inhibitors for LUTS. The odds ratio (OR), mean difference (MD) and surface under the cumulative ranking curve (SUCRA) were calculated with the GeMTC R package.

Results: Twenty randomized trials with 4131 patients were included in this network meta-analysis. Based on the SUCRA values, vardenafil (10 mg) combined with α-blockers ranked first, first and sixth; sildenafil (25 mg) combined with α-blockers ranked second, third and first; and tadalafil (20 mg) combined with α-blockers ranked third, second and fourth in IPSS, post void residual, and maximum flow rate, respectively.

Conclusions: Combination therapy with α-blockers and phosphodiesterase-5 inhibitors was effective and well tolerated for LUTS. For men who prioritize high efficacy, vardenafil (10 mg) combined with α-blockers seems to be the treatment of choice. For men wishing to optimize minimally invasive treatment, sildenafil (25 mg) and tadalafil (20 mg) combined with α-blockers appears to have a possible advantage in terms of avoiding adverse effects.

Abbreviations: BPH = benign prostatic hyperplasia, ED = erectile dysfunction, IPSS = International Prostate System Score, LUTS = lower urinary tract symptoms, PDE5Is = phosphodiesterase 5 inhibitors, PVR = post void residual, Qmax = maximum flow rate, TRAEs = treatment-related adverse events.

Keywords: lower urinary tract symptoms, α-blockers, phosphodiesterase type 5 inhibitors, network meta-analysis

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LQ, ZX and ZF contributed equally as co-first authors of this manuscript.

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1. Introduction

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) are prevalent conditions that have negative impacts on quality of life and self-confidence.[1,2] The prevalence of LUTS in men aged over 50 years old has been reported to be more than 50%.[3] Based on the pathophysiological relationships between BPH-LUTS and ED, several studies have confirmed that both diseases often coexist and have a growing prevalence with age.[4,5]

The European Association of Urology guidelines proposed α-adrenergic blockers as the first-line therapy for the treatment of BPH-LUTS. Nevertheless, phosphodiesterase-5 inhibitors (PDE5Is), including sildenafil, vardenafil, and tadalafil, are currently present the first line effective pharmacotherapy options for patients with ED. Recently, several studies have suggested that treatment with PDE5Is cures BPH-LUTS because BPH-LUTS and ED share a similar pathophysiological pathway. Although recent studies have demonstrated that PDE5Is can effectively treat LUTS, the administration of PDE5Is and treatment-related adverse events remain unclear.[6,7]

Oral PDE5Is were first approved for the treatment of ED in 1998. The mechanism of action involves the PDE5I-induced increase in the level of the second messenger cyclic guanosine monophosphate, which promotes smooth muscle relaxation and induces penile erection. In theory, PDE5Is can increase the level of nitric oxide in smooth muscle, which in turn relaxes the smooth muscle of urinary organs (such as the bladder neck and the prostate) and ultimately relieves the symptoms of LUTS associated with BPH.

Studies have shown that combination therapy with PDE5Is and α-blockers provided better outcomes than α-adrenergic blocker monotherapy. In our analysis, studies related to combination therapy consisting of α-blockers and different PDE5Is were identified and systemically evaluated, with the aim of providing a basis for the future clinical treatment of LUTS.

2. Methods

2.1. Literature search

This systematic review complied with the Preferred Reporting Items for Systematic Review and Meta-analysis Statement (PRISMA Statement, www.prisma-statement.org).[8,9] This study protocol was registered in PROSPERO with ID CRD42020163756. Ethical approval and informed consent were not required due to all data was extracted from previous published trials. Searches were carried out in 3 electronic databases, namely, Cochrane Library, PubMed and EMBASE, from January 1988 to December 2019. Studies were conducted to compare the efficacy and treatment-related adverse events of combination therapy consisting of α-blockers and different PDE5Is, and there was no limitation on language or publication. The search strategies included the keywords "α-blockers", "phosphodiesterase type 5 inhibitors" and "lower urinary tract symptoms" and MeSH terms.

2.2. Study selection

Randomized clinical trials (RCTs) that were conducted to compare the efficacy or the treatment-related adverse events of combination therapy consisting of α-blockers and different PDE5Is were included. The included studies fit the following criteria: (1) RCTs and (2) patients received LUTS treatment with combination therapy consisting of α-blockers and PDE5Is for at least 1 month. The exclusion criteria were as follows:

(1) reviews, opinions, editorials, case reports, conference abstracts or animal models; and
(2) Non English full text available.

The following 4 outcomes were assessed:

(1) International Prostate System Score (IPSS);
(2) maximum flow rate (Qmax);
(3) post void residual (PVR); and
(4) treatment-related adverse events (TRAEs).

2.3. Data extraction and study quality assessment

The data were extracted by 2 independent researchers (LQ and ZFH). Discrepancies between reviewers were resolved by a third reviewer (LQZ). The methodological quality of the eligible studies was assessed with the Cochrane Collaboration tool.

2.4. Statistical analysis

R was used to perform a network meta-analysis with a random-effect model. The network meta-analysis was constructed to perform indirect comparisons between monotherapy with either α-blockers or PDE5Is and the combination therapy of an α-blockers plus a PDE5I. The rank probabilities of combination therapy consisting of α-blockers and different PDE5Is were assessed with a cumulative ranking curve (SUCRA). R (V.3.5.1), with the packages gemtc (V.0.8) and Open BUGS (V.3.2.3), was used for all computations.

3. Results

3.1. Description of included studies

In total, 5515 studies were identified and screened, and 20 studies were ultimately included in this meta-analysis after full text retrieval, analysis and selection[3,10–28] (Fig. 1, Table 1, Supplementary Figures 7 to 8, http://links.lww.com/MD/F70, http://links.lww.com/MD/F71). Among the 20 studies, 12 focused on Asian populations,[10,11,13–15,20–25,28] 3 focused on European populations,[16–18] 2 focused on North American populations,[19,26] 1 focused on South American populations,[27] 1 focused on an African population[3] and the last is a multicenter study.[12] For the IPSS assessment, 9 studies[3,10,15,17,18,20,22–24] were included in the network meta-analysis. For the IPSS assessment, 9 studies[5,10,15,17,18,20,22–24] were included in the network meta-analysis. For the PVR assessment, 8 studies[10,13,15,18,20,22,24,25] were included in the network meta-analysis. For the Qmax assessment, 8 studies[3,15,18,20,22–25] were included in the network meta-analysis. And for the TRAEs assessment, 17 studies[3,10–14,16,18–24,26–28] were included in the network meta-analysis. The characteristics of the trials are described in Table 1.

3.2. IPSS

Compared with α-blockers, vardenafil (10 mg) combined with α-blockers (MD: −3.8; 95% CI −7.0 – −0.59), sildenafil (25 mg) combined with α-blockers (MD: −1.5; 95% CI −4.1 – −1.2), and tadalafil (20 mg) combined with α-blockers (MD: −0.76;

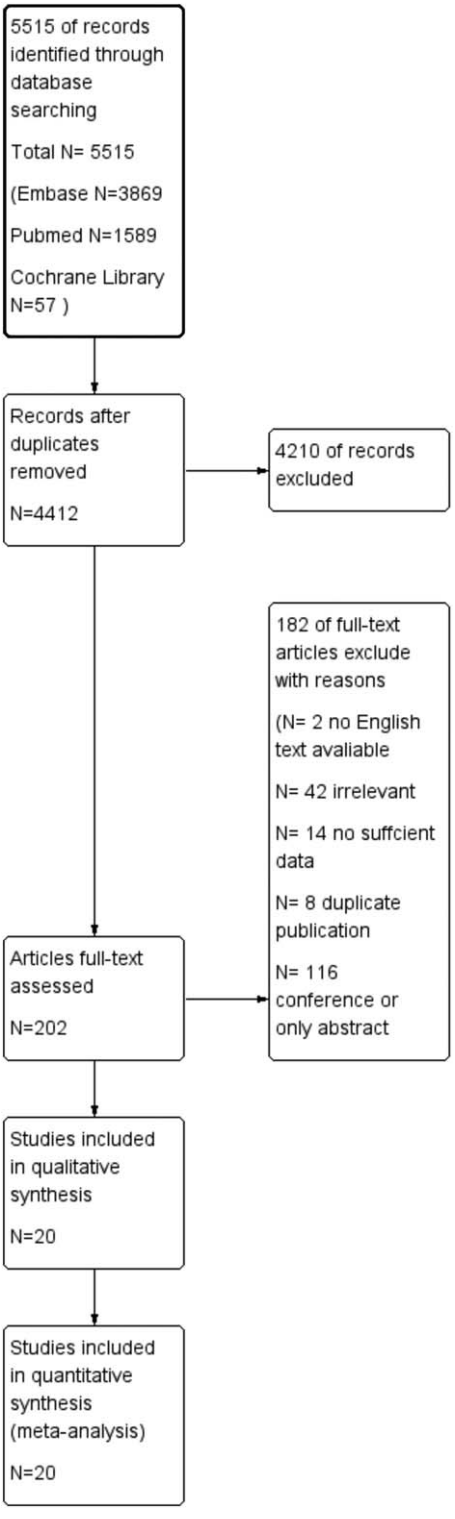

Figure 1. Flow chart of the systematic review (according to PRISMA Click statement).

95% CI −2.6 – 0.89) were more effective at improving IPSS (Fig. 2). As indicated by the SUCRA analysis, vardenafil (10 mg) combined with α-blockers has the highest probability of improving the IPSS (SUCRA: 0.037) (Fig. 2, Supplementary Figs. 1, http://links.lww.com/MD/F64).

3.3. PVR

As shown in Figure 3, vardenafil (10 mg) combined with α-blockers had a significantly higher PVR outcome (MD: −13. 0; 95% CI −38.0 – 11.0) than the other treatments. SUCRA analysis suggested that vardenafil (10 mg) and tadalafil (20 mg) combined with α-blockers have the highest probability of improving the PVR, with SUCRA values of 0.0937 and 0.27, respectively (Figs. 3–4, Supplementary Figs. 2, http://links.lww.com/MD/F65).

3.4. Qmax

As shown in Figure 7, sildenafil (25 mg) combined with α-blockers resulted in a significantly higher Qmax (MD: 2.5; 95% CI 0.54–4.9) than the other drugs. SUCRA analysis suggested that sildenafil (25 mg) combined with α-blockers has the highest probability of improving the Qmax, with a SUCRA value of 0.9072 (Fig. 5, Supplementary Figs. 3, http://links.lww.com/MD/F66).

3.5. Treatment-related adverse events

The TRAEs of combination therapy consisting of α-blockers and different PDE5Is were generally mild (Fig. 6).

3.6. Network assumptions

The node-splitting method and Bayesian P value were used to report the inconsistency of our results. However, the node-splitting method could not be implemented by reporting its Bayesian P value because direct and indirect comparisons do not exist in the same arm for IPSS, Qmax and PVR (Supplementary files Fig. 4-6, http://links.lww.com/MD/F67, http://links.lww.com/MD/F68, http://links.lww.com/MD/F69).

4. Discussion

Studies have shown that PDE5Is combined with α-blockers are superior to α-blocker monotherapy with regard to improving the symptoms of LUTS, and the adverse events of the combined treatment are not clinically important. A previous meta-analysis concluded that combination therapy with α-blockers and PDE5Is can significantly improve LUTS when compard with monotherapy, especially having an advantage in IPSS.[7] In the largest study to date, Zhang et al found that compared with monotherapy, combination therapy with α-blockers and PDE5Is is efficacious and well tolerated in the treatment of LUTS and ED.[14]

In this network meta-analysis, we systematically reviewed the efficacy and safety of monotherapy with either α-blockers or PDE5Is and the combination therapy of an α-blockers plus PDE5I. There were 2 major findings in our study:

(1) combination therapy with an α-blocker plus a PDE5I was significantly more effective than α-blockers monotherapy at improving LUTS.
(2) Based on the network meta-analysis and SUCRA analysis, vardenafil (10 mg) combined with α-blockers, sildenafil (25 mg) combined with α-blockers and tadalafil (20 mg) combined with α-blockers appear to be better choices than monotherapies with either α-blockers or PDE5Is and other combination therapies of α-blockers plus PDE5Is in terms of efficacy.

Table 1

Study characteristics.

Study	Study type	Intervention arms: number of patients	Follow-up schedule	Primary outcome assessed
Pattanaik et al (2019)[10]	RCT	Group A: 20 patients, Tadalafil 10 mg Group B: 20 patients, tamsulosin 0.4 mg Then crossover	18 wk	IPSS IIEF PVR Qmax Adverse events
Kim et al (2011)[11]	RCT	Group A: 51 patients, placebo Group B: 51 patients, tadalafil 5 mg Group C: 49 patients, tamsulosin 0.2 mg	12 wk	IPSS Qmax PVR Adverse events
Oelke et al (2012)[12]	RCT	Group A: 172 patients, placebo Group B: 171 patients, tadalafil 5 mg Group C: 168 patients, tamsulosin 0.4 mg	12 wk	IPSS BII Qmax IIEF Adverse events
Yokoyama et al (2012)[13]	RCT	Group A: 154 patients, placebo Group B: 151 patients, tadalafil 2.5 mg Group C: 155 patients, tadalafil 5 mg Group D:152 patients, tamsulosin 0.2 mg	12 wk	IPSS Qmax PVR PSA Adverse events
Zhang et al (2019)[14]	RCT	Group A: 361 patients, placebo Group B: 362 patients, tadalafil 2.5 mg Group C: 185 patients, tamsulosin 0.2 mg	12 wk	IPSS IIEF Qmax SEP 2 SEP 3 Adverse events
Ozturk et al (2012)[15]	RCT	Group A: 50 patients, alfuzosin XL 10 mg Group B: 50 patients, alfuzosin XL 10 mg + sildenafil 50 mg	12 wk	IPSS IIEF-ED QoL Qmax PVR PSA
Bechara et al (2008)[16]	RCT	Group A: 15 patients, tamsulosin 0.4 mg + tadalafil 20mg Group B: 15 patients, tamsulosin 0.4 mg + placebo Then crossover	90 d	IPSS IPSS-QoL Qmax PVR IIEF-EF GAQ VAS adverse events
Cantoro et al (2013)[17]	RCT	Group A: 20 patients, tamsulosin 0.4 mg Group B: 24 patients, tamsulosin 0.4 mg + sildenafil 50 mg (at demand, at least twice a week)	60 d	IPSS NIH-CPSI IIEF-5
Fawzi et al (2017)[3]	RCT	Group A: 75 patients, tamsulosin 0.4 mg + sildenafil 25 mg Group B: 75 patients, tamsulosin 0.4 mg + placebo	6 mo	IPSS IPSS QoL Qmax IIEF-5
Gacci et al (2012)[18]	RCT	Group A: 30 patients, tamsulosin 0.4 mg + vardenafil 10 mg Group B: 30 patients, tamsulosin 0.4 mg + placebo	12 wk	IPSS IPSS-bother IIEF-5 OAB-q Qmax, Qave PVR
Goldfischer et al (2012)[19]	RCT	2 wk placebo lead-in period + a-blocker Group A: 158 patients, a-blocker + tadalafil 5 mg Group B: 159 patients, a-blocker + placebo	12 wk	Dizziness adverse events

(*continued*)

Table 1

(continued).

Study	Study type	Intervention arms: number of patients	Follow-up schedule	Primary outcome assessed
Karami et al (2016) [20]	RCT	Group A: 61 patients, tadalafil 20 mg	12 wk and 12 wk extension period	IPSS
		Group B: 61 patients, tamsulosin 0.4 mg		IIEF
		Group C: 61 patients, tadalafil 20 mg + tamsulosin 0.4 mg		IPSS
				subscores
				Qmax
				PVR
				GAQ
Kim et al (2017)[21]	RCT	Group A: 153 patients, tamsulosin 0.4 mg + tadalafil 5 mg	12 wk and 12 wk extension period	IPSS
		Group B: 164 patients, tamsulosin 0.2 mg + tadalafil 5 mg		IIEF
		Group C: 162 patients, tadalafil 5 mg Then all groups: tamsulosin 0.4 mg + tadalafil 5 mg for 12 wk		Qmax
				PVR
				GAQ
Kumar et al (2013)[22]	RCT	Group A: 25 patients, alfuzosin 10 mg	3 mo	IPSS
		Group B: 25 patients, tadalafil 10 mg		IPSS
		Group C: 25 patients, alfuzosin 10 mg + tadalafil 10 mg		voiding and storage subscores
				Qmax
				PVR
				IPSS
				QoL
				IIEF-EF
Liguori et al (2009) [23]	RCT	Group A: 22 patients, alfuzosin 10 mg	12 wk	IIEF-EF
		Group B: 21 patients, tadalafil 20mg		IPSS
		Group C: 23 patients, alfuzosin 10 mg + tadalafil 20 mg		Qmax
				Qave
Singh et al (2014) [24]	RCT	Group A: 45 patients, tamsulosin 0.4 mg	3 mo	IPSS
		Group B: 44 patients, tadalafil 10 mg		IIEF-5
		Group C: 44 patients, tamsulosin 0.4 mg + tadalafil 10 mg		IPSS
				QoL
				Qmax
				PVR
Tuncel et al (2009)[25]	RCT	Group A: 20 patients, sildenafil 25 mg	8 wk	IPSS
		Group B: 20 patients, sildenafil 25 mg + tamsulosin 0.4 mg		Qmax
		Group C: 20 patients, tamsulosin 0.4 mg		PVR
				SHIM IIEF (3rd and 4th questions)
Kaplan et al (2007)[26]	RCT	Group A: 20 patients, alfuzosin 10 mg	12 wk	IPSS
		Group B: 21 patients, sildenafil 25 mg		Qmax
		Group C: 21 patients, alfuzosin 10 mg + sildenafil 25 mg		PVR
				IIEF
				Frequency and nocturia (voiding diary)
Regadas et al (2012) [27]	RCT	Group A: 20 patients, tadalafil 5 mg + tamsulosin 0.4 mg	30 d	UDS (PdetQmax, Qmax, BOOI, detrusor overactivity) IPSS
		Group B: 20 patients, tamsulosin 0.4 mg + placebo		
Sharifi et al (2014)[28]	RCT	Group A: 55 patients, tamsulosin 0.4 mg + sildenafil 50mg	3 mo	Prostate volume
		Group B: 55 patients, tamsulosin 0.4 mg + placebo		PVR

BOOI = Bladder outlet obstruction index, IIEF = International index of erectile function, IPSS = International Prostate System Score, PVR = post void residual, Qmax = maximum flow rate, QOL = quality of life, RCT = randomized control trial, SHIM = Sexual health inventory for male, TRAEs = treatment-related adverse events, UDS = urodynamics.

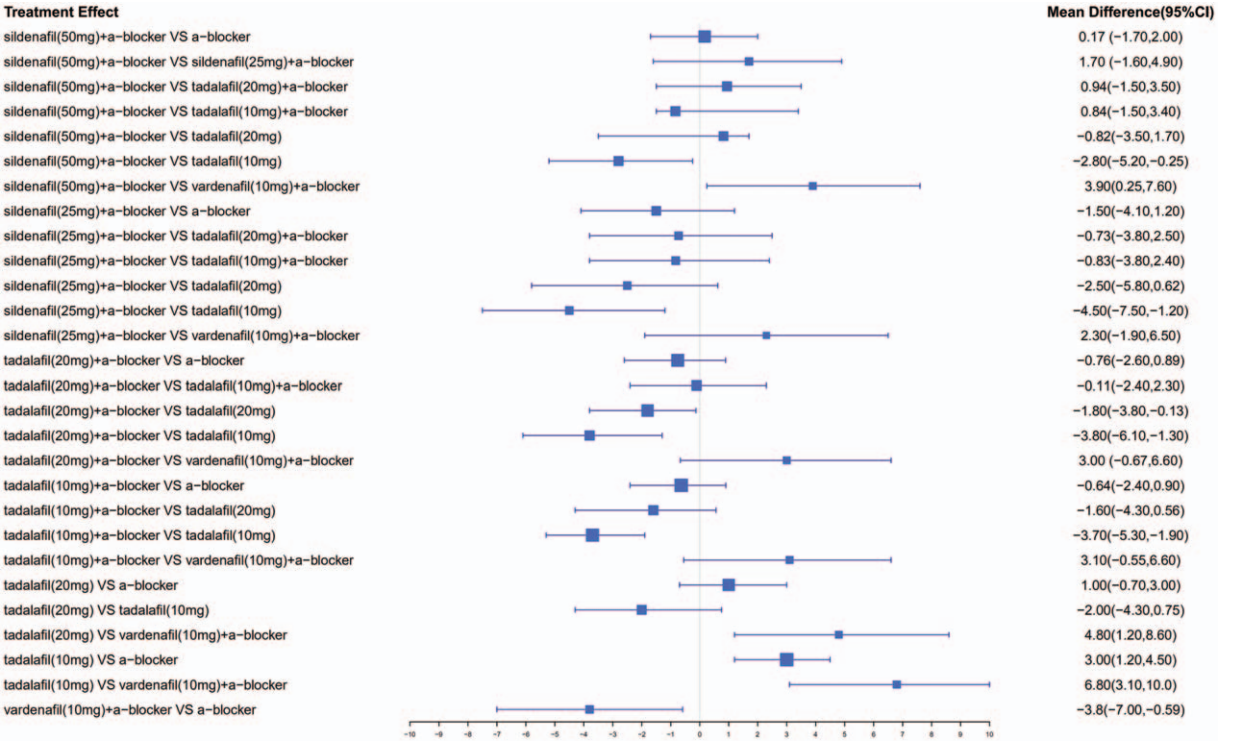

Figure 2. Estimates of effects for comparisons of combination therapy consisting of a-blocker and diferent phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms on the outcome IPSS.

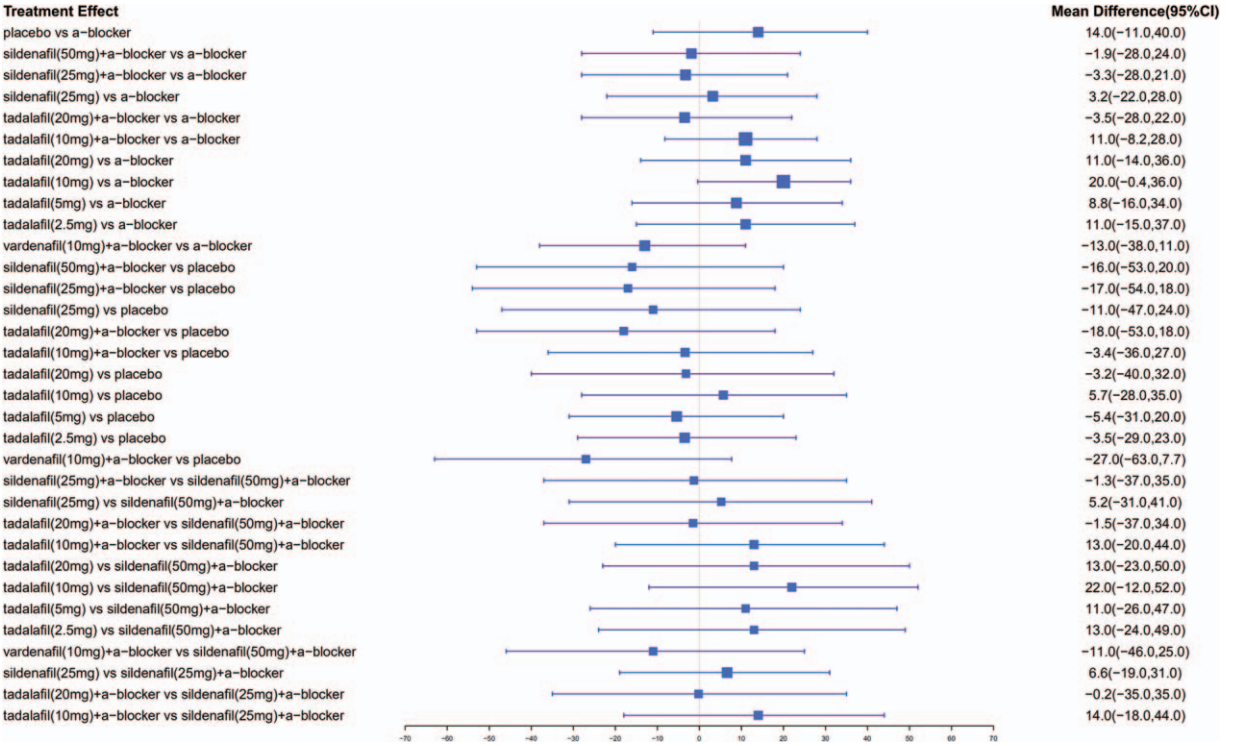

Figure 3. Estimates of effects for comparisons of combination therapy consisting of a-blocker and diferent phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms on the outcome PVR (A). PVR = post void residual.

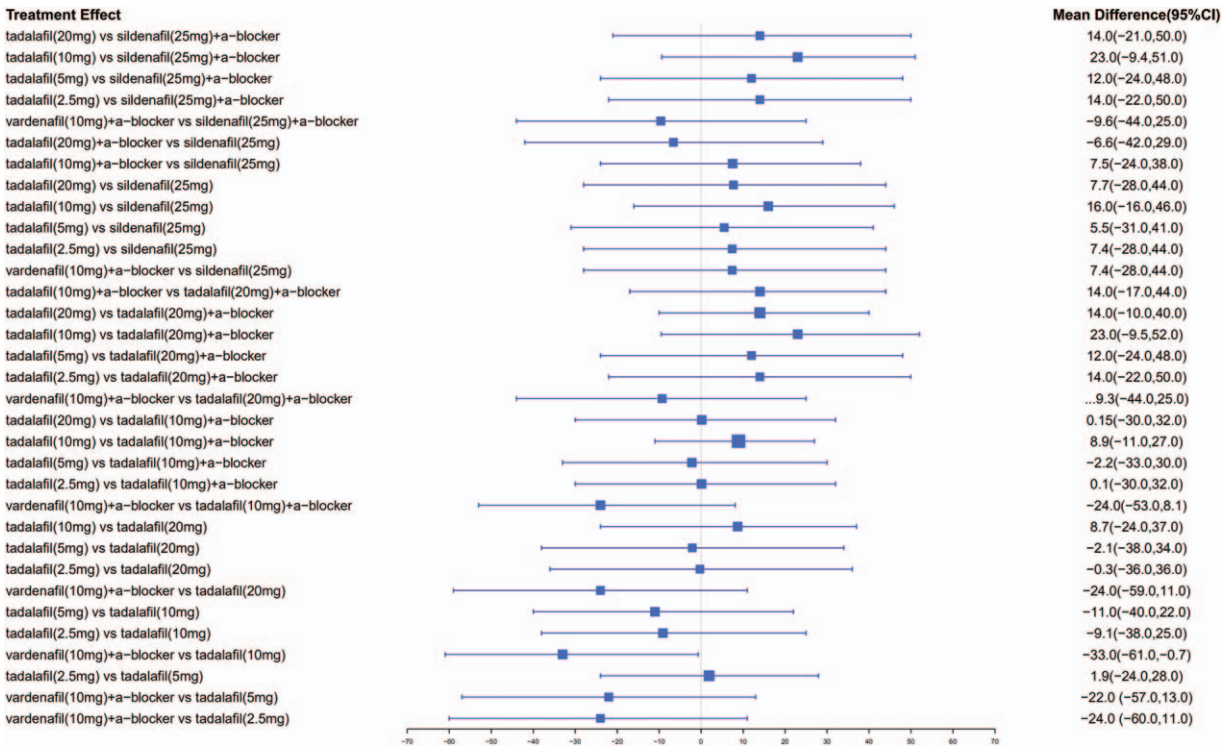

Figure 4. Estimates of effects for comparisons of combination therapy consisting of a-blocker and diferent phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms on the outcome PVR (B). PVR = post void residual.

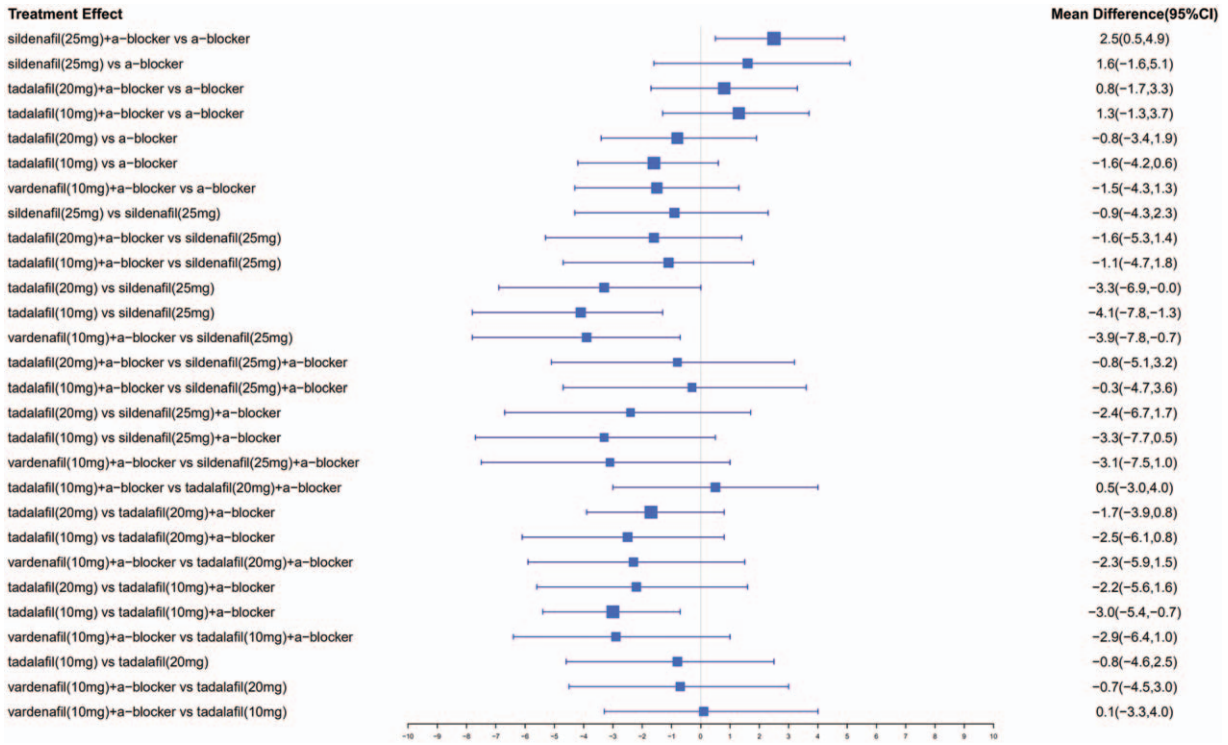

Figure 5. Estimates of effects for comparisons of combination therapy consisting of a-blocker and diferent phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms on the outcome Qmax.

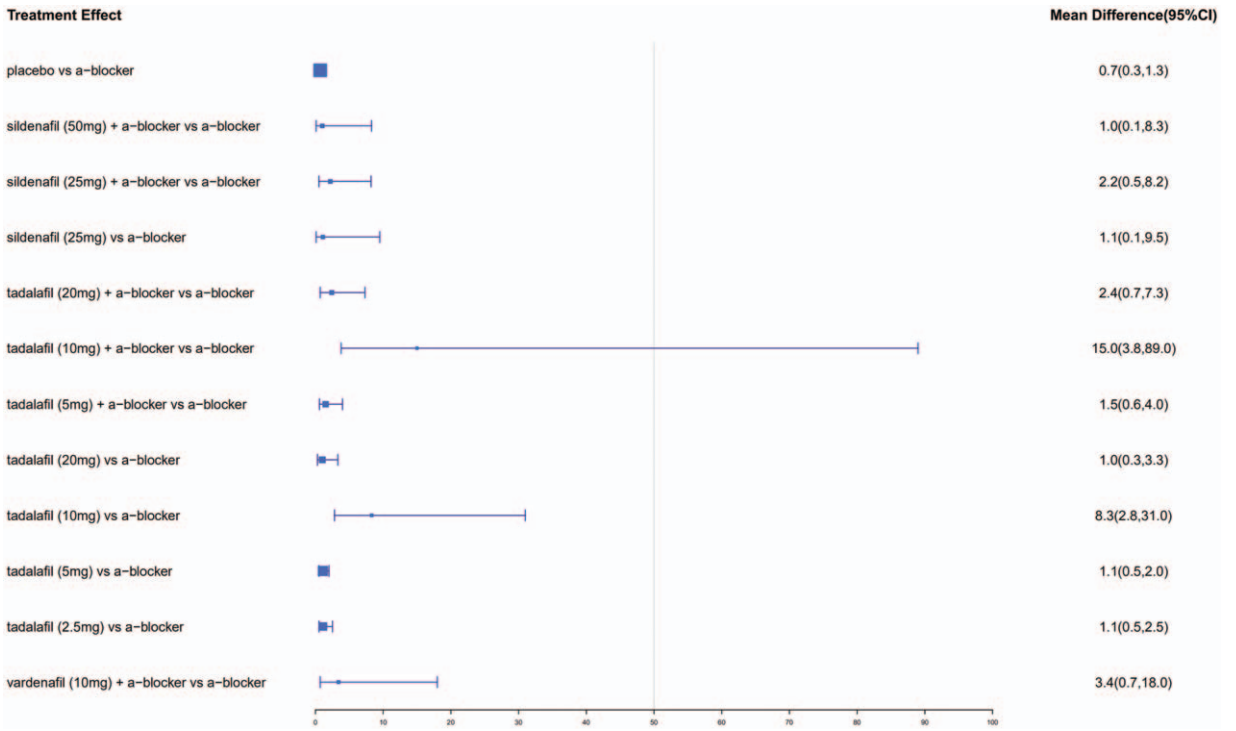

Figure 6. Estimates of effects (with 95% credible intervals) and confidence ratings for TRAEs. TRAEs = treatment-related adverse events.

This network meta-analysis presents a systemic study to comprehensively compare monotherapy with either α-blockers or PDE5Is and combination therapy with an α-blockers and a PDE5I. Our results were consistent with many previous studies. For instance, Zhang et al,[6] in their study concluded that combination therapy with α-blockers and PDE5Is significantly improved the IPSS, Qmax and IIEF. However, that review did not compare different combination therapies, nor did it restrict treatment time. Another previous meta-analysis comparing combination therapy with α-blockers and PDE5Is with monotherapy suggested that combination therapy improved LUTS.[7] Previous NMAs[29,30] comparing phosphodiesterase type 5 inhibitors combined with tamsulosin among the general population suggested that sildenafil combined with tamsulosin is superior to other administrations. In our study, however, sildenafil (25 mg) combined with α-blockers is not proven to be superior to other administrations.

5. Limitations

Several limitations of the present study should be discussed. First, because direct and indirect comparisons do not exist in the same arm for IPSS, Qmax and PVR, the node-splitting method could not be implemented by reporting its Bayesian P value, which might have affected the quality of the current results. Second, the small number of included studies might have affected the validity of our results. Third, other uncommon regimens were excluded from our network meta-analysis.

6. Conclusions

In conclusion, combination therapy with α-blockers and PDE5Is was significantly more effective than α-blocker monotherapy at improving LUST. Among the combinations, vardenafil (10 mg) combined with α-blockers, sildenafil (25 mg) combined with α-blockers and tadalafil (20 mg) combined with α-blockers appear to be better choices than monotherapies with either α-blockers or PDE5Is and other combination therapies of α-blockers plus PDE5Is in terms of efficacy. However, our present results need to be verified with more high-quality studies with comprehensive data.

Author contributions

All authors have read and approved the manuscript.

LIU Qiangzhao: Project development, Data Collection, Data analysis, Manuscript writing. LIAN Qiong: Data collection. ZHOU Fenghai: Data collection. ZHANG Xiaofeng: Manuscript writing. ZHANG Fa: Manuscript writing. XI Xinsheng: Manuscript writing; GUO Bohong: Manuscript writing.

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Methodology: Liu Qiangzhao.
Software: Liu Qiangzhao.
Writing – original draft: Liu Qiangzhao, Lian Qiong, Zhou Fenghai, Zhang Xiaofeng, Zhang Fa, Guo Bohong, Xi Xinsheng.
Writing – review & editing: Liu Qiangzhao, Zhang Xiaofeng.

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