

Original Article

Efficacy and safety of PDE5-Is and α -1 blockers for treating distal ureteral calculi: a mixed treatment comparison network meta-analysis of randomized controlled clinical trials

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Abstract: Background and aims: Ureteral calculi are frequent diseases in urology. Medical expulsive therapy is one of the standard treatments, but the efficacy is still controversial. The goal of this study was to investigate the efficacy and safety of monotherapy or combination therapy with alpha-blockers and phosphodiesterase 5 inhibitors for in the treatment of distal ureteral calculi. Methods: Randomized controlled trials as of July 2018 were searched from PubMed, Cochrane Library, Web of Science, and Embase to compare the above drug categories for patients with distal ureteral calculi using appropriate search strategies. An inverse variance model was used for the comparison of mixed treatments. The calculi expulsion rate (SER) is the primary and the calculi expulsion time (SET) is the primary-secondary outcome measure. Results: This network meta-analysis included 11 trials involving 1509 participants, which indicated that tamsulosin (RR: 2.46; 95% CI, 1.05-6.21), tadalafil (RR: 4.08; 95% CI, 1.78-9.98), silodosin (RR: 7.28; 95% CI, 2.48-21.87), tadalafil combined with tamsulosin (RR: 6.33; 95% CI, 1.83-20.18), and tadalafil combined with silodosin (RR: 20.25; 95% CI, 3.93-97.23) has a significant higher calculi expulsion rate compared with placebo, and network comparisons indicated that tadalafil (RR: 1.64; 95% CI, 1.07-2.65), silodosin (RR: 2.75; 95% CI, 1.44-5.65), tadalafil combined with tamsulosin (RR: 2.45; 95% CI, 1.05-5.45), and tadalafil combined with silodosin (RR: 7.47; 95% CI, 1.72-32.92) has a significantly higher calculi expulsion rate compared with tamsulosin. At the same time, this network meta-analysis shows that tadalafil combined with silodosin is significantly shorter than other treatments in terms of calculi expulsion time. A comparison of the side effects of tamsulosin and tadalafil showed that the tadalafil group had higher headache, dizziness, backache, and orthostatic hypotension than the tamsulosin group. Further, there was no evidence of statistical heterogeneity between studies ($P > 0.05$). It is interesting that tadalafil significantly improved ejaculation abnormalities in male patients compared with tamsulosin ($P < 0.05$). Conclusion: In conclusion, alpha-blockers, PDE5-Is, PDE5-Is combined with alpha-blockers significantly increased the expulsion rate of distal ureteral calculi. Among these interventions, tadalafil combined with silodosin is likely to be "best". At the same time, tadalafil combined with silodosin may further shorten the expulsion time of distal ureteral calculi.

Keywords: Alpha-blockers, phosphodiesterase 5 inhibitors, tadalafil, sildenafil, tamsulosin, silodosin, distal ureteral calculi, meta-analysis, bayes theorem

Introduction

Urinary calculi are one of the most common diseases of the urinary tract. The prevalence rate has gradually increased to nearly 20% in recent

decades [1, 2]. Approximately 22% of urinary calculi are located in the ureter, of which approximately 68% are located distal to the ureter [3]. The incidence of ureteral calculi is high and complications are numerous [4]. Many studies

report that up to 50% of patients with ureteral calculi can expel ureteral calculus by themselves. The expulsion rate for ureteral calculi < 5 mm in diameter can be as high as 85%, and the expulsion time is mostly between 28 and 40 days [5, 6]. Improvements in minimally invasive surgery have significantly changed the treatment of ureteral calculus when spontaneous expulsion has not occurred. Such surgery is not only risky but also expensive. Medical expulsive therapy (MET) has now become a definitive treatment.

Commonly used medical expulsive therapy (MET) drugs in clinical practice include traditional Chinese medicine, anticholinergic drugs such as 654-2, calcium ion antagonists, alpha-blockers, and steroids [7]. Alpha-blockers can inhibit ureteral muscle contraction, reduce basal muscle tone, and reduce peristaltic rate [8]. Among them, tamsulosin has been proven to increase the rate of calculi expulsion and reduce the expulsion time, so it has been widely used in clinical practice [9, 10]. Previous high-quality meta-analyses have shown that the use of alpha-blockers in patients with ureteral calculus can increase calculi expulsion rates and shorten calculi expulsion time [11, 12]. Recently, a large multicenter randomized controlled trial (RCT) reveals that tamsulosin and nifedipine are not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks for patients with expectantly managed ureteric colic [13].

Previous studies have identified the presence of nitric oxide fibers in the distal ureter and confirmed the relaxation of the nitric oxide pathway on ureteral smooth muscle [13]. Since then, researchers have looked at how to use the nitric oxide pathway so that it can be effectively implemented in clinical practice until the emergence of phosphodiesterase 5 inhibitors (PDE5-Is). PDE5 isoenzymes have now been identified in a variety of tissues in animals and humans. They have been demonstrated in smooth muscle cells such as corpus cavernosum, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, spinal cord, cerebellum, pancreas, prostate, urethra, and bladder [16-18].

In recent years, more and more evidence suggests that PDE5-Is may be a new target for the treatment of distal ureteral calculus [3, 19-28].

Direct meta-analysis showed that PDE5-Is can effectively treat distal ureteral calculi as a MET. Drug therapy with tadalafil alone or in combination with tamsulosin for the treatment of distal ureteral calculi is safe, effective, and well tolerated. However, because these analyses were limited by comparators and under-research, a meta-analysis of direct comparisons among PDE5-Is, alpha-blockers, and placebo was impossible.

Network meta-analysis overcomes this limitation by creating indirect comparisons and allowing data to be synthesized, which may serve to find the most effective measures [29, 30]. Therefore, a meta-analysis and systematic evaluation of Bayesian networks were performed to discover both direct and indirect comparisons of alpha-blockers, PDE5-Is, and PDE5-Is plus alpha-blockers. To this end, changes in distal ureteral calculi expulsion rate and expulsion time were compared. In addition, a comparative study of the adverse effects of tamsulosin (alpha-blockers) and tadalafil (PDE5-Is) was analyzed.

Material and methods

Inclusion and exclusion criteria

Published RCTs that meet the following criteria were included: Evaluate the efficacy and safety of PDE5Is, alpha-blockers in the treatment of distal ureteral calculi, and provide adequate analytical data. The primary outcome variables were the calculi expulsion rate and calculi expulsion time during the treatment period. Secondary variables were mainly adverse drug reactions. No language restrictions apply. These articles were excluded as follows: (1) review or meta-analysis articles; (2) repeated or updated data; (3) comments, editorials, letters, and case reports.

Search strategy

Randomized controlled trials as of July 2018 were searched from PubMed, Cochrane Library, Web of Science, and Embase. In addition, cross-reference searches were performed on the list of references in eligible articles to examine research articles not found during computerized searches. All citations and abstracts selected by the search strategy were independently screened by the two authors to identify

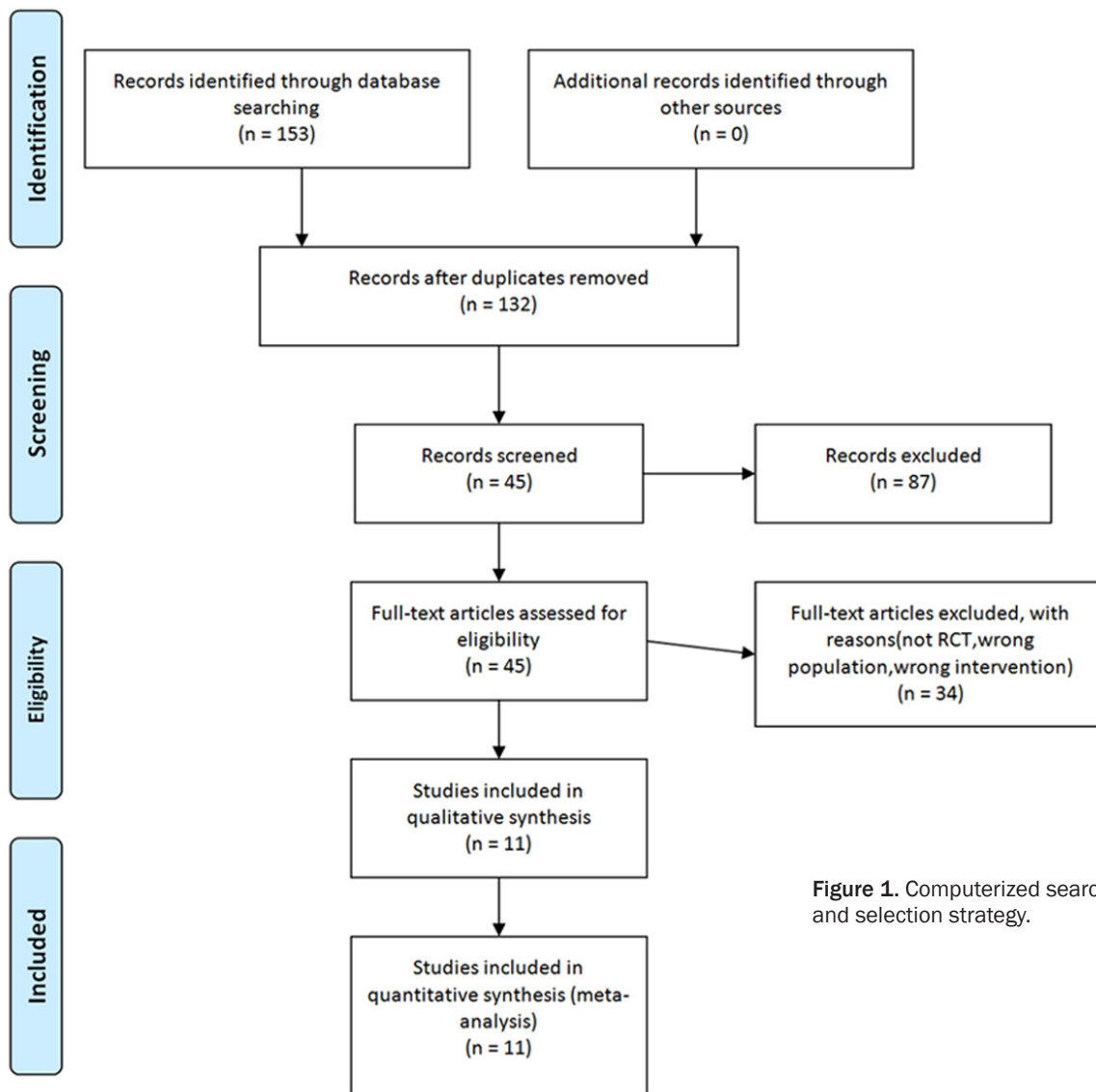


Figure 1. Computerized search and selection strategy.

studies that might be eligible. Searches were done for a combination of keywords: Alpha-blockers, Phosphodiesterase 5 inhibitors, Tadalafil, Sildenafil, Tamsulosin, Silodosin, Distal ureteral calculi.

Data collection and analysis

Two researchers independently assessed the quality of the study and extracted the data and Cochrane was used as a risk of bias in RCT quality assessment tool. Quality assessment was performed using Review Manager 5 (Rev-Man 5.3). A summary estimate of the effect was obtained using a random effects model, and the results are expressed as the hazard

ratio (RR) and 95% confidence interval (CI) for the two-category results, and the mean difference (MD) and 95% CI for the continuous results. Sensitivity analysis was performed to remove poor methodological studies. The results were sorted and an estimate of the likelihood that a treatment will be the best treatment was generated.

Statistical analysis

Outcome variables measured at specific time points were compared in terms of mean differences with 95% CIs using a network meta-analysis. Analyses were based on non-informative priors for effect sizes and precision. The prob-

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Table 1. Enrolled studies for this meta-analysis

Study	No. of patients	Age, years	Gender (Male/female)	Stone size (mm)	Mean stone size (mm)	Stone location	Intervention/control	Follow-up (day)
Shokeir et al. (2016)	50	45.3 ± 10.83	NA	5-10	NA	Distal	Sildenafil 50 mg/dia	28
	50	45.8 ± 13.72	NA		NA		Placebo	28
Abhishek et al. (2015)	50	NA	NA	4-10	NA	Juxtavesical	Tadalafil 10 mg/dia	28
	50	NA	NA		NA		Tamsulosin 0.4 mg/dia	28
Kumar et al. (2015)	50	NA	NA		NA		Placebo	28
	90	37.5 ± 13.5	67/23	5-10	NA	Distal	Tadalafil 10 mg/dia	28
	90	36.4 ± 10.03	62/28		NA		Tamsulosin 0.4 mg/dia	28
	90	36.73 ± 12	64/26		NA		Silodosin 8 mg/dia	28
Hasan et al. (2011)	30	29.8 ± 10.8	14/16	5-10	7.91	Juxtavesical	Tadalafil 10 mg/dia	14
	30	30.6 ± 9.3	13/17	6-10	7.55		Placebo	14
KC et al. (2016)	44	32.05 ± 13.34	24/20	5-10	7.13 ± 1.5	Distal	Tadalafil 10 mg/dia	14
	41	31.37 ± 11.98	27/14		7.09 ± 1.2		Tamsulosin 0.4 mg/dia	14
Puvvada et al. (2016)	100	36.34 ± 11.32	65/35	5-10	7.10 ± 1.43	Distal	Tadalafil 10 mg/dia	28
	100	37.53 ± 12.67	67/33		7.22 ± 1.25		Tamsulosin 0.4 mg/dia	28
Kumar	31	35.23 ± 13.54	025/6	5-10	6.67 ± 1.44	Distal	Tadalafil 10 mg + tamsulosin 0.4 g/dia + prednisolone 5 mg	42
	31	32.45 ± 9.36	019/12		7.05 ± 1.62		Tamsulosin 0.4 g/dia + prednisolone 5 mg	42
Jayant et al. (2014)	122	37.23 ± 12.54	67/55	5-10	7.05 ± 1.62	Distal	Tadalafil 10 mg + tamsulosin 0.4 mg/dia	28
	122	36.45 ± 10.36	65/57		6.72 ± 1.44		Tamsulosin 0.4 mg/dia	28
Goyal et al. (2018)	62	42.61 ± 14.93	41/21	6-10	7.60 ± 0.91	Distal	Tadalafil 10 mg/dia	28
	62	42.13 ± 13.18	43/18		7.54 ± 1.11		Tamsulosin 0.4 mg/dia	28
Celik et al. (2018)	30	46.3 ± 9.9	30/0	0-10	4.7 ± 1.8	Distal	Tadalafil 5 mg/dia	42
	34	43.9 ± 11.5	34/0		4.5 ± 1.8		Tamsulosin 0.4 mg/dia	42
	35	39.2 ± 11	35/0		4.5 ± 1.7		Silodosin 8 mg/dia	42
Rahman et al. (2018)	40	38 ± 10	24/16	5-10	7.5 ± 1.20	Distal	Tamsulosin 0.4 mg/dia	28
	40	34 ± 12	22/18		7.4 ± 1.30		Silodosin 8 mg/dia	28
	40	35 ± 10	25/15		7.6 ± 1.35		Silodosin 8 mg/dia + tadalafil 5 mg/dia	28

NA, not available.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abhishek et al. 2015	?	?	?	?	+	+	+
Celik et al. 2018	?	?	?	?	+	+	+
Goyal et al. 2018	+	+	?	?	+	+	+
Hasan et al. 2011	+	?	?	+	+	+	+
Jayant et al. 2014	+	+	+	+	+	+	+
KC et al. 2016	+	+	?	?	+	+	+
Kumar et al. 2014	+	+	?	+	+	+	+
Kumar et al. 2015	+	+	+	+	+	+	+
Puwada et al. 2016	+	+	+	+	+	+	+
Rahman et al. 2018	+	+	?	?	+	+	+
Shokeir et al. 2016	+	+	+	+	+	+	+

Figure 2. Risk of Bias Assessment. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Five trials exhibited a low risk of bias for all quality criteria, and two studies were classified as having a high risk of bias.

ability of each group of clinical event rates was assessed by Bayesian Markov Chain Monte Carlo modeling. Convergence and lack of auto-correlation were confirmed after four chains and a 50,000-simulation burn-in phase. The basic network structure diagram is drawn based on the data included in the article. The second is to list the direct and indirect comparison results between related drugs in tabular form and ultimately the ranking of the effects of the intervention. Review Manager 5.3, STATA 14.0 and R (R version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>) and the meta for and gemtc packages were used for all statistical analysis.

Results

Search strategy results

In total, 153 records were found through our database searches. No other records were identified by other sources. Among them, 87 records were excluded according to the title and abstract in the initial screening stage. For the remaining 45 studies, we conducted a full-text screening based on criteria, resulting in 11 independent studies (involving 1509 randomized patients) included in the study. The PRISMA research selection flowchart is shown in **Figure 1**.

Study characteristics and quality assessment

Data corresponding to confounding factors in each study are summarized in **Table 1**. One study was the comparison between sildenafil and placebo [19]. One study was the comparison between tadalafil and placebo [22], and one trial reported the results of a three-arm trial comparing tadalafil, tamsulosin, and placebo [20]. Two trials reported the results of a three-arm trial comparing tadalafil, tamsulosin, and silodosin [21, 27]. Three trials reported comparisons between tadalafil and tamsulosin [23, 24, 26]. Two trials reported a comparison between tadalafil and tamsulosin and tamsulosin [3, 25]. One trial reported the results of a three-arm trial comparing tadalafil with silodosin, tamsulosin, and silodosin [28]. The selected study included 1,509 patients, and 11 studies evaluated the ureteral calculus expulsion rate as the primary outcome at 14-42 days. Most studies have reported expulsion time as one of the secondary outcome reports, and some of them provide information on side effects during treatment.

Figure 2 presents details of the quality assessment, as measured by the biasing tool for Cochrane Collaboration Risk. At least one of the seven studies was judged as an unclear risk of bias, which showed that the two studies were classified as having a high risk of bias [20, 27]. Four studies had a risk of moderate bias [22, 23, 26, 28]. Only one study had a lower risk of bias in quality standards [3]. Eight studies on reporting appropriate allocation concealment methods were clear [3, 19, 21, 23-26, 28], and only six studies reported blind methods of the result assessors [3, 19, 21, 22, 24, 25].

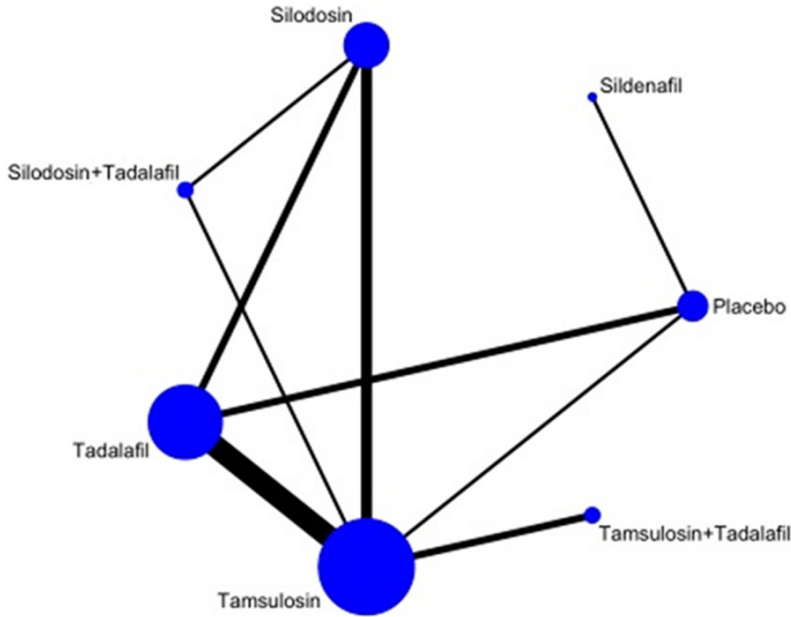


Figure 3. Network plot of eligible comparisons for the stone expulsion rate.

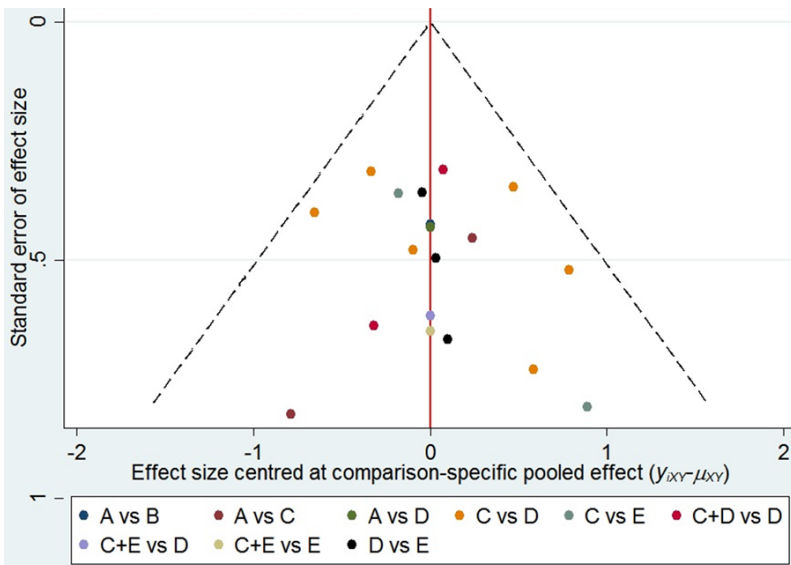


Figure 4. Funnel plots from pairwise meta-analysis for the stone expulsion rate. A: Placebo; B: Sildenafil; C: Tadalafil; D: Tamsulosin; E: Silodosin.

Effects of interventions

The effect of drugs on the calculi expulsion rate (SER): The network plot of eligible comparisons for the stone expulsion rate is shown in **Figure 3**. Funnel plots from pairwise meta-analysis are demonstrated in **Figure 4**, however, with few studies, it was difficult to assess publication bias, although some degree of bias is suspected.

Assessing primary outcome, the results of a pairwise meta-analysis suggested that tadalafil (relative risk [RR]: 1.10; 95% confidence interval [CI], 1.01, 1.20), silodosin (RR: 1.25; 95% CI, 1.10-1.42), and tadalafil combined with tamsulosin (RR: 1.24; 95% CI, 1.09-1.42) has a significant higher calculi expulsion rate compared with tamsulosin. Furthermore, the results of the paired meta-analysis showed silodosin (RR: 1.16; 95% CI, 1.02-1.33) showed a significant higher calculi expulsion rate compared with tadalafil.

This network meta-analysis indicated that all treatments except sildenafil were more effective than placebo. Specifically, tamsulosin (RR: 2.46; 95% CI, 1.05-6.21), tadalafil (RR: 4.08; 95% CI, 1.78-9.98), silodosin (RR: 7.28; 95% CI, 2.48-21.87), tadalafil combined with tamsulosin (RR: 6.33; 95% CI, 1.83-20.18), and tadalafil combined with silodosin (RR: 20.25; 95% CI, 3.93-97.23) had a significantly higher calculi expulsion rate With placebo, and network comparisons indicated that tadalafil (RR: 1.64; 95% CI, 1.07-2.65), silodosin (RR: 2.75; 95% CI, 1.44-5.65), tadalafil combined with tamsulosin (RR: 2.45; 95% CI, 1.05-5.45),

and tadalafil combined with silodosin (RR: 7.47; 95% CI, 1.72-32.92) had a significant higher calculi expulsion rate compared with tamsulosin. Direct and indirect comparison of the calculi expulsion rate is shown in the lower and upper triangles of **Table 2**, with significant differences underlined and bolded. The ranking results indicate that tadalafil combined with silodosin is the most effective treatment to promote calculi expulsion, followed by silodosin,

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Table 2. The direct and indirect comparison of the stone expulsion rate

Placebo	3.08 (0.95, 9.81)	2.46 (1.05, 6.21)	4.08 (1.78, 9.98)	7.28 (2.48, 21.87)	6.33 (1.83, 20.18)	20.25 (3.93, 97.23)
NA	Sildenafil	0.80 (0.19, 3.67)	1.33 (0.32, 5.96)	2.29 (0.47, 11.81)	2.04 (0.37, 10.22)	6.49 (0.88, 47.52)
NA	NA	Tamsulosin	1.64 (1.07, 2.65)	2.75 (1.44, 5.65)	2.45 (1.05, 5.45)	7.47 (1.72, 32.92)
NA	NA	0.89 (0.81, 0.97)	Tadalafil	1.67 (0.81, 3.52)	1.48 (0.56, 3.66)	4.72 (0.97, 19.81)
NA	NA	0.82 (0.72, 0.93)	0.86 (0.75, 0.98)	Silodosin	0.87 (0.30, 2.46)	2.82 (0.69, 11.44)
NA	NA	0.80 (0.71, 0.92)	NA	NA	Tadalafil + Tamsulosin	3.30 (0.61, 15.73)
NA	NA	NA	NA	NA	NA	Tadalafil + Silodosin

NA, not available.

Table 3. Ranking probability of the drugs to promote stone expulsion rate

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Placebo	0	0	0	0	0	0.04	0.95
Sildenafil	0.02	0.07	0.1	0.16	0.28	0.35	0.03
Tamsulosin	0	0	0	0.02	0.37	0.59	0.02
Tadalafil	0	0.02	0.14	0.57	0.26	0.01	0
Silodosin	0.05	0.55	0.3	0.08	0.02	0	0
Tadalafil + Tamsulosin	0.07	0.28	0.42	0.15	0.06	0.01	0
Tadalafil + Silodosin	0.86	0.08	0.04	0.02	0	0	0

tadalafil combined with tamsulosin, tadalafil, tamsulosin, sildenafil, and placebo. The ranking probability of the drugs to promote calculi expulsion rate is shown in **Table 3** and **Figure 5**.

The effect of drugs on the calculi expulsion time (SET): The network plot of eligible comparisons for the stone expulsion time is shown in **Figure 6**. Funnel plots from pairwise meta-analysis are demonstrated in **Figure 7**, however, with few studies, it was difficult to assess publication bias, although some degree of bias is suspected.

Assessing the second outcome, the pair-wise meta-analysis showed that tadalafil (standard mean difference [SMD]: 1.38; 95% credible interval [CI], 0.67-2.1) and tadalafil combined with tamsulosin (SMD: 2.02; 95% CI, 0.81-3.23) has a significantly shorter calculi expulsion time compared with tamsulosin.

However, this network meta-analysis indicated that tadalafil (SMD: 2.04; 95% CI, -4.99-1.12) and tadalafil combined with tamsulosin (SMD: 2.78; 95% CI, -2.33-7.94) had no significant shorter calculi expulsion time compared with tamsulosin. Interestingly, this network study shows that tadalafil combined with silodosin is significantly shorter than other treatments in terms of calculi expulsion time.

The direct and indirect comparison of the calculi expulsion time is shown in the lower and upper triangles of **Table 4**, with significant differences underlined and bolded. The ranking results indicate that tadalafil combined with silodosin is the most effective treatment to reduce calculi expulsion time, followed by tadalafil combined with tamsulosin, silodosin, tadalafil, tamsulosin. The ranking probability of the drugs to reduce calculi expulsion time is shown in **Table 5** and **Figure 8**.

Safety

Four studies [21, 23, 24, 26] compared the adverse effects of the tadalafil and tamsulosin groups. Although the pooled results of our four studies showed that patients in the tadalafil group had higher headache, dizziness, backache, and orthostatic hypotension than the tamsulosin group, there were no statistically significant differences in these results (**Figure 9**). A meta-analysis of three studies [21, 23, 26] revealed that the incidence of ejaculation abnormalities was significantly lower in males in the tadalafil group than in the tamsulosin group ($P < 0.05$). Furthermore, the final summary showed that there was no statistically significant difference between the tadalafil group and the tamsulosin group ($P > 0.05$). All results regarding the incidence of adverse events were

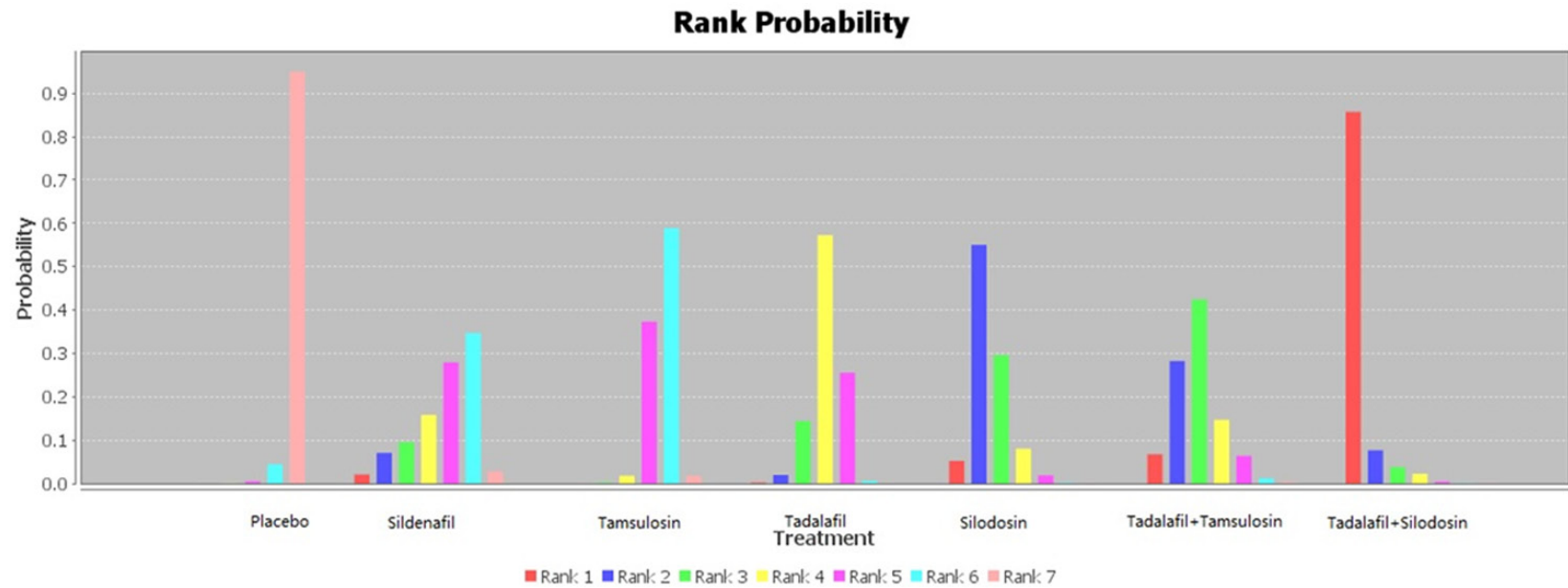


Figure 5. Ranking probability of the drugs to promote stone expulsion rate.

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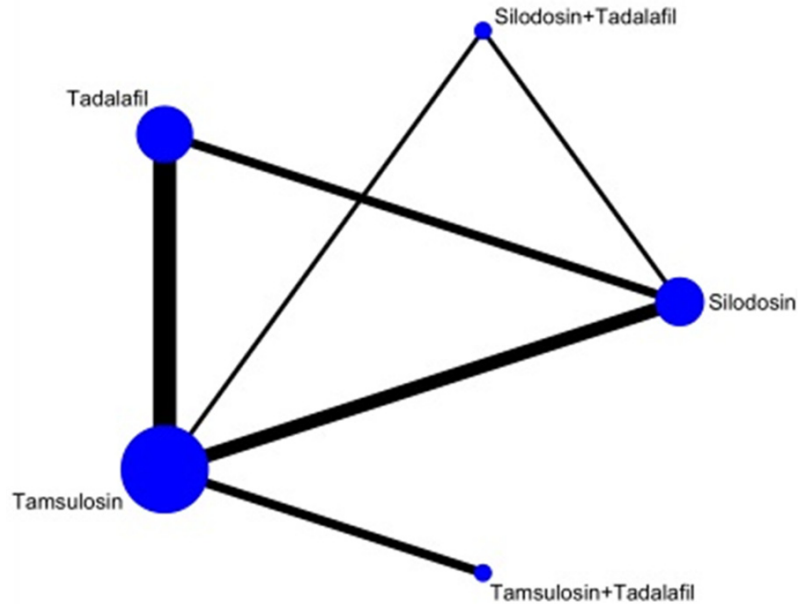


Figure 6. Network plot of eligible comparisons for stone expulsion time.

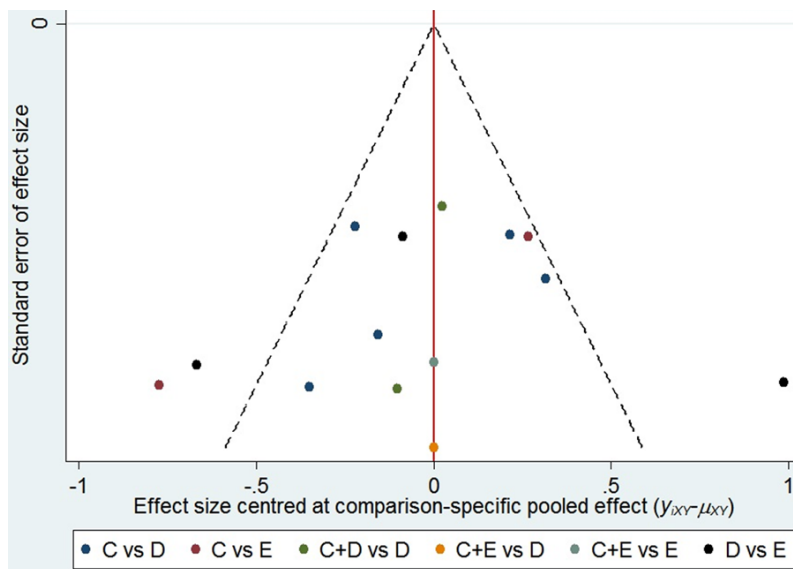


Figure 7. Funnel plots from pairwise meta-analysis for the stone expulsion time. C: Tadalafil; D: Tamsulosin; E: Silodosin.

not affected by the use of random effects models.

Discussion

Recent studies have estimated that the prevalence of the US population is 10.6% for men and 7.1% for women [31]. Similarly, cases of ureteral calculus have increased similarly, with high morbidity and mortality in calculi patholo-

gy reflected in the high cost of health systems (about \$2 billion per year in the United States) [1]. Urinary calculi often recur, and the lifetime recurrence rate is about 50% [32]. The recurrence rate is about 10% in 1 year, 35% in 5 years, and 50% in 10 years [33]. Therefore, medical expulsion therapy (MET) is a cost-effective treatment widely used for ureteral calculus [34].

Studies have shown that tamsulosin can act on the bladder neck and prostate urethra receptors, thereby relaxing the smooth muscles of various parts of the calculi expulsion pathway, which promotes the expulsion of calculus and inhibits the stimulation of smooth muscle spasm and bladder triangle. Treatment also reduced frequent urination and urgency [35] and in this study it was shown to promote the passage of distal ureteral calculus and relieve renal colic [36]. Therefore, if the ureter smooth muscle can be sequentially and rhythmically contracted, it is beneficial to the expulsion of ureteral calculus.

PDE5-Is act on the lower urinary tract and PDE5 inhibitors are recognized as first-line treatments for erectile dysfunction [37-39]. The mechanism is based on the relaxation of smooth muscle cells in the penile tissue, and the distribution of smooth muscle cells in the prostate, bladder, and ureter muscles [40, 41]. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important intracellular second messengers that mediate cellular responses. An increase in cAMP and cGMP triggers a signal transduction cascade. PDE5Is

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Table 4. The direct and indirect comparison of the stone expulsion time

Tamsulosin 1.38 (0.67, 2.1) NA	-2.04 (-4.99, 1.12) Tadalafil NA	-2.16 (-5.79, 2.05) -0.12 (-4.24, 4.37) Silodosin NA	-2.78 (-7.94, 2.33) -0.70 (-6.95, 5.28) -0.57 (-7.40, 5.62) Tadalafil + Tamsulosin NA	-19.02 (-25.02, -12.69) -16.95 (-23.42, -10.26) -16.79 (-22.98, -11.02) -16.30 (-24.20, -7.95) Tadalafil + Silodosin
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NA, not available.

Table 5. Ranking probability of the drugs to reduce stone expulsion time

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Tamsulosin	0	0	0.04	0.21	0.74
Tadalafil	0	0.22	0.39	0.33	0.06
Silodosin	0	0.28	0.35	0.26	0.1
Tadalafil + Tamsulosin	0	0.49	0.21	0.2	0.1
Tadalafil + Silodosin	1	0	0	0	0

acts on the nitric oxide-mediated smooth muscle pathway, and cyclo phosphodiesterase 5 (PDE5) degrades cyclic nucleotides (cAMP and cGMP). The NO/cGMP/PDE5 pathway can be pharmacologically affected by inhibition of PDE5, and therefore, the use of PDE5 inhibitors can contribute to smooth muscle relaxation by preserving cAMP and cGMP in relaxing ureteral smooth muscle [42, 43]. Al-Aown et al. [44] used a domestic pig to make a ureter model for *in vitro* studies to demonstrate that vardenafil relaxes the ureteral smooth muscle in a dose-dependent manner, and the cGMP level in smooth muscle tissue after treatment is increased by about 3-fold. Kc and colleagues [23] reported that 75% of patients felt mild penile erections for 20-30 minutes after ingesting tadalafil, and no patients had abnormal penile erections. Kumar and colleagues [25] found that 12.9% of the tadalafil plus tamsulosin group improved compared with the tamsulosin group alone. Two recent studies evaluated the effects of sexual intercourse in the output of distal ureteral calculi and found that married men with distal ureteral calculi who had 3-4 strokes per week had an increased expulsion rate. This effect may be related to the release of nitric oxide during sexual intercourse, which causes the ureter to relax [45, 46].

In 2018, Xifeng Sun and colleagues [47] reported a meta-analysis comparing the efficacy and safety of PDE5-Is and alpha-1 blockers in the treatment of lower ureteral calculi or LUTS. It

shows that tadalafil may have better drainage effect and shorter expulsion time than tamsulosin. The meta-analysis is the first time meta-analysis of the network evaluation of clinical trials of PDE5-Is and alpha-blockers and to determine the efficacy of PDE5-Is in MET. In conclusion, this study indicates that alpha blockers, phosphodiesterase 5 inhibitors, and

alpha-blockers plus Phosphodiesterase 5 inhibitors are superior in promoting calculi expulsion rates compared with placebo except for sildenafil. However, it is not excluded that the inclusion of sildenafil research literature is small, and there may be publication bias. When used in this way, tadalafil combined with silodosin significantly reduced the time of calculi removal.

Although the pooled results of these four studies showed that patients in the tadalafil group had higher headache, dizziness, backache, and orthostatic hypotension than the tamsulosin group, there were no statistically significant differences in these results. The incidence of ejaculation abnormalities was significantly lower in males in the tadalafil group than in the tamsulosin group.

The advantages of this study are reproduced below. The Bayesian framework was used to compare PDE5-Is, alpha-blockers, or PDE5-Is combined with alpha-blockers, and the results show that PDE5-Is combined with Alpha-blockers may be an effective and safe treatment. Statistical rankings were used to suggest that tadalafil combined with silodosin may be the best option for the treatment of distal ureteral calculus.

Although this study is the first meta-analysis of a network evaluation of PDE5-Is and alpha-blockers clinical trials, there continue to be

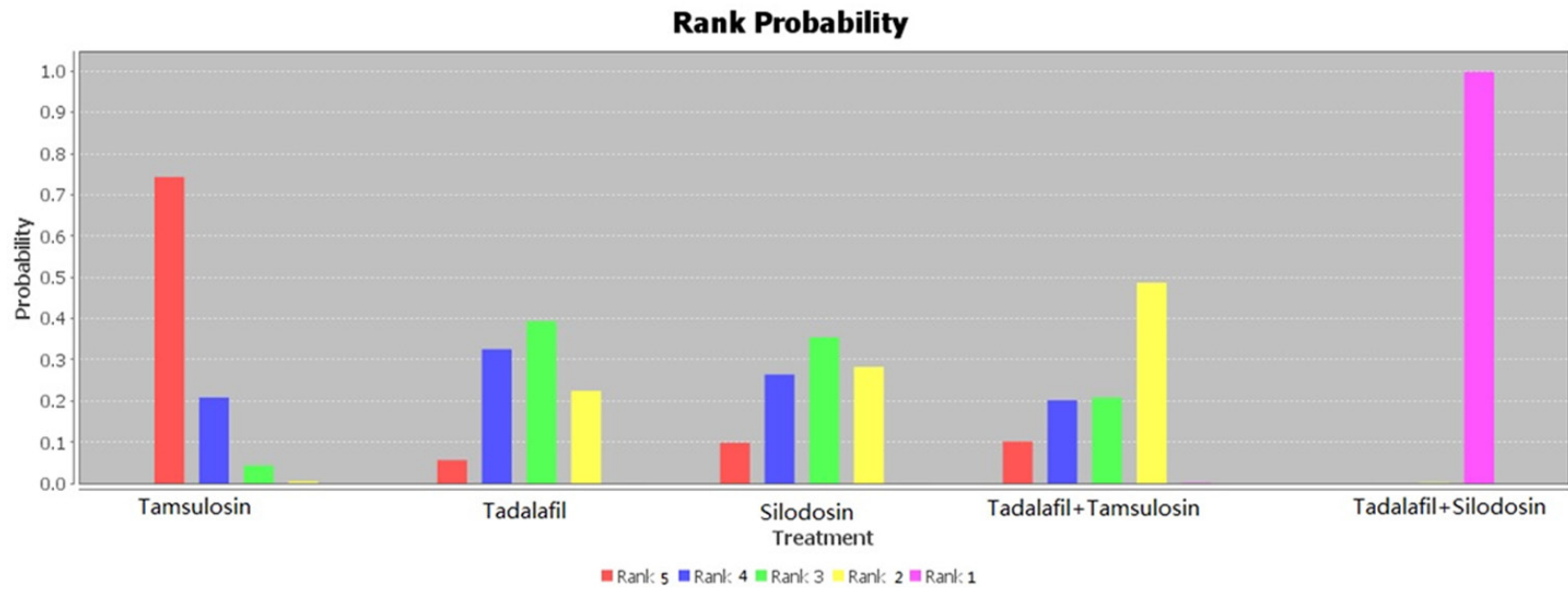


Figure 8. Ranking probability of the drugs to promote stone expulsion time.

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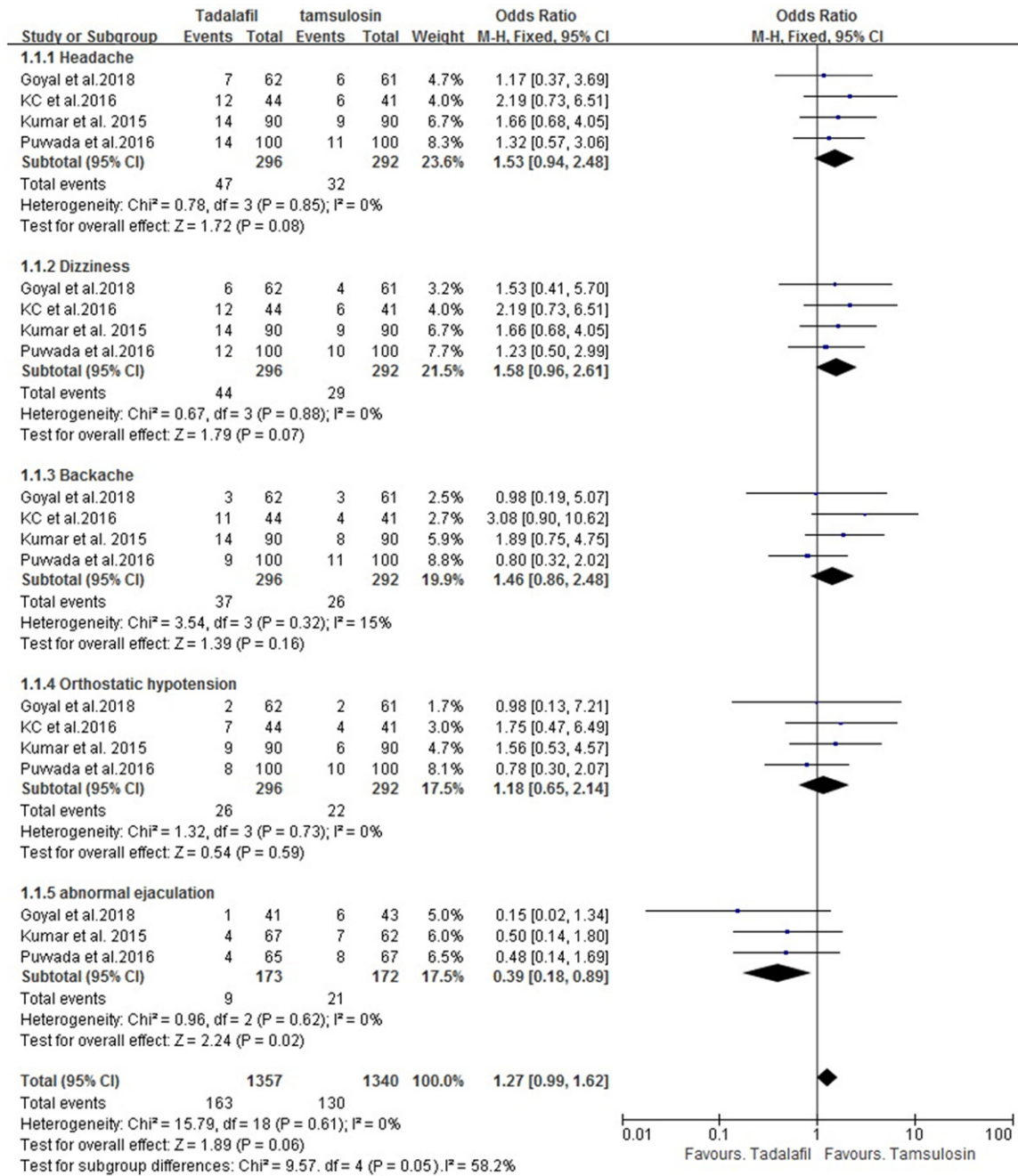


Figure 9. Pooled estimate of drug-related adverse effects between tadalafil and tamsulosin.

some limitations. First, despite the fact that we have collected all eligible studies, there are only 11 RCTs, and the sample size is not large enough, this may increase the likelihood of type I and type II errors. Second, positive research results are more likely to be published rather than negative; these results may be influenced by publication bias. Third, only two studies evaluated the combination of ureteral calculi, and only one article compared sildenafil treatment

with small sample size. Finally, the most extensive study did not assess the effect of tadalafil on the frequency of sexual intercourse in the study population, which also had a potential effect on the spontaneous expulsion of distal ureteral calculus.

Conclusion

Alpha-blockers, PDE5-Is, and PDE5-Is combined with alpha-blockers significantly increased

the expulsion rate of distal ureteral calculi. Among these interventions, tadalafil combined with silodosin is likely to be “best”. At the same time, tadalafil combined with silodosin may further shorten the expulsion time of distal ureteral calculi. Due to the limited number of included studies and the small sample size, further elaborate double-blind multi-center RCTs are strongly encouraged to deal with clinical issues.

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Disclosure of conflict of interest

None.

Abbreviations

Abs, Adrenoceptor 1 blockers; AEs, Adverse events; cGMP, Cyclic-guanine monophosphate; cAMP, Cyclic-adenosine monophosphate; CI, Confidence interval; ED, Erectile dysfunction; NO, Nitric oxide; RR, Relative risk; PDE5-Is, Phosphodiesterase 5 inhibitors; RCT, Randomized controlled trials; SM, Smooth muscle; MD, Mean difference.

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