

Effect of the symptom-based alpha-blocker treatment on lower urinary tract symptoms in women: systematic review and meta-analysis

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Abstract

Aims: The aim of this study was to evaluate the effects of alpha blockers in women with lower urinary tract symptoms.

Methods: We conducted systematic review and meta-analysis on published *a priori* protocols. We searched multiple data sources for published and unpublished randomized controlled trials in any language. Primary outcomes included urologic symptom scores, quality of life, and overall adverse events. We performed meta-analysis using RevMan 5.3 and rated the certainty of evidence using Grading of Recommendations, Assessment, Development, and Evaluation.

Results: Alpha blockers likely reduced urological symptom score (mean difference: -1.50 , 95% confidence interval: -2.91 to -0.09 ; moderate certainty of evidence). Alpha blockers may improve quality of life (standardized mean difference: -0.35 , 95% confidence interval: -0.85 to 0.15 ; low certainty of evidence) and have little to no difference in overall adverse events (risk ratio: 1.09 , 95% confidence interval: 0.55 to 2.15 ; low certainty of evidence). Based on five studies comparing combination therapy with alpha blockers and anticholinergics to anticholinergic monotherapy, combination therapy likely results in little to no difference in urological symptom score (mean difference: -0.35 , 95% confidence interval: -1.98 to 1.27 ; moderate certainty of evidence) and quality of life (mean difference: -0.11 , 95% confidence interval: -0.48 to 0.27 ; moderate certainty of evidence). We are very uncertain about the effect of combination therapy on overall adverse events (risk ratio: 1.07 , 95% confidence interval: 0.40 to 2.84 ; very low certainty of evidence).

Conclusion: Alpha blocker monotherapy for the women with lower urinary tract symptoms regardless of the underlying cause likely has satisfactory efficacy compared with placebo. However, combination therapy with anticholinergics likely has no additional effect on urologic symptom score and quality of life compared with anticholinergic monotherapy.

Keywords: adrenergic alpha-antagonist, lower urinary tract symptoms, meta-analysis, women

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Introduction

Alpha-blockers have been used to treat lower urinary tract symptoms (LUTS) in women. However, there is no sufficient verification regarding the use of alpha blockers for the treatment of

LUTS in women. In general, alpha blockers have been considered for the treatment of female voiding dysfunction (FVD). FVD is caused by acontractile or underactive detrusor activity and bladder outlet obstruction (BOO). Clinically,

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alpha blockers have been considered to treat functional BOO in women because alpha blockers reduce outlet resistance.¹⁻³

The diagnosis of BOO is often challenging in women. Women with BOO present with frequent urination and urgency as well as voiding LUTS. Therefore, urodynamic study (UDS), imaging, and cystoscopy can help to find women with BOO. Women with a peak flow rate (Q_{max}) <15 ml/s combined with detrusor pressure at a peak flow rate ($P_{det}Q_{max}$) >20 cmH₂O in a UDS can be diagnosed with female BOO (FBOO).⁴ However, the lack of a standard definition of FBOO might contribute to decreasing the quality of clinical studies to evaluate the treatment effect of alpha blockers on FBOO. Therefore, we performed a systematic review and meta-analysis to examine the effect of alpha blockers on LUTS in women.

Materials and methods

We performed this systematic review and meta-analyses according to published protocol in PROSPERO (CRD42018098875).

We carried out a comprehensive search through multiple databases of EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials in the Cochrane Library (CENTRAL), Latin American and Caribbean Health Sciences Literature (LALICS), SCOPUS, as well as trials registry (www.clinicaltrials.gov/), WHO International Clinical Trials Registry Platform, other source of gray literature report (www.greylit.org/), and conference proceedings (Supplement 1). We also searched references of identified studies for supplemental studies and contacted authors of identified studies for reports of any unpublished or published studies, including new, additional studies, or works in progress.

We initially performed the search on 8 May 2018 and then performed the updated search on 26 August 2021. Two review authors (S.J.K. and T.W.K.) independently screened all potentially related records and classified studies according to the criteria provided in the Cochrane Handbook for Systematic Review of Interventions.⁵ We included randomized controlled trials (RCTs), including pseudo-RCTs regardless of their language of publication or publication status.

Types of participants

Women clinically diagnosed with LUTS were included in this review. We excluded trials of women with underlying distinct disorders such as urinary tract infection, cerebrovascular disease, myelopathy, spinal injury, or surgery-related urinary disorders.

Types of intervention

We compared alpha blockers monotherapy or combination therapy with other treatment *versus* other treatment in LUTS such as placebo, behavioral modifications, anticholinergics, β -agonist, or cholinergics.

Types of outcomes measured

We set the primary outcomes of this review as urological symptom scores, quality of life (QoL), overall adverse events, and the secondary outcomes as acute urinary retention, Q_{max} , and post-void residual (PVR). We considered outcomes measured for 2 months or less (short term) and 12 months or longer (long term) separately. We considered clinically important differences for review outcomes to rate certainty of the evidence for imprecision in the ‘Summary of findings’ tables.

Assessment of risk of bias in included studies

The risk of bias of each included study was evaluated by two review authors (S.J.K., T.W.K.) independently. We settled all debates through discussion and agreements. We measured risk of bias using the Cochrane ‘Risk of bias’ assessment tool. We assessed risk of bias domains as ‘low risk’, ‘high risk’, or ‘unclear risk’ and evaluated individual bias items as explained in the Cochrane Handbook for Systematic Reviews of Interventions.⁵

Data collection and data extraction

All studies are independently evaluated by two review authors (S.J.K. and T.W.K.) using a data extraction format. A domain-based bias risk assessment was performed as described in the Cochrane Handbook for Systematic Reviews of Interventions.

Authors tried to get the number and sum of events in the population for dichotomous outcomes and mean with the standard deviation or data needed

to calculate this information for continuous outcomes.⁵

We summarized data using a random-effects model. We planned to statistically assess heterogeneity using the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered low, moderate, and high, respectively.⁶ The funnel plot asymmetry test is usually performed only if the meta-analysis contains at least 10 studies. However, the number of contained studies was consistently too small to conduct this type of analysis. We executed statistical analysis using Review Manager 5 software (The Cochrane Collaboration, Copenhagen, Denmark).

Secondary analysis

We planned to assess subgroup analyses with investigation of interactions based on participant age (under 65 years *versus* 65 years and older) and neurodynamic status (BOO *versus* detrusor underactivity). In addition, we planned to carry out sensitivity analyses to explore the influence of risk of bias on effect sizes.

Summary of findings table

We submitted the overall certainty of evidence (CoE) for each outcome according to Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), which takes into account five criteria related not only to internal validity (study limitations, inconsistency, imprecision, publication bias) but also to external validity such as directness of results.⁷

Results

Search results

We identified 1519 records through electronic database searching, including two records from other sources [NCT00679315 (Lee 2018 protocol clinicaltrials.gov), Yamanishi 2003 (Yamanishi 2004 abstract)]. We found no records in the gray literature repository, and reference lists of retrieved included trials and reviews. After removing the duplicates, we screened the titles and abstracts of 1133 records and excluded 1090. We screened 46 full-text articles and excluded 29 articles (Supplement 2). We included 11 studies (14 records) that ultimately met the inclusion criteria in the qualitative synthesis of this review. The flow of literature through this assessment

process is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1).

Included studies

Table 1 presents the baseline characteristics of the included studies with 1257 total randomized participants.^{8–21} The average age of the patients ranged from 32.9 to 62.8 years. Average baseline urological symptom scores measured by International Prostate Symptom Score (IPSS) ranged from 12.7 to 32.9. Average baseline Qmax ranged from 9.9 to 29.2 ml/s and average baseline PVR ranged from 14.4 to 24.0 ml. Most of the studies included women with LUTS of a total IPSS more than 8 or symptoms of overactive bladder for more than 3 months. Major exclusion criteria included LUTS from recent acute urinary retention, urinary tract infection, neurological disease, or previous pelvic surgery or radiation. We only found the studies with short-term follow-up (up to 12 months).

Of 11 studies, 4 studies were published in Czech, Chinese, or Japanese. The remaining were published in English. We tried to get in touch with the corresponding authors of the included trials to make additional information on study methodology and outcomes and received replies from four studies.^{8–10,20}

We had three comparisons in this review, five studies of which compared alpha blockers monotherapy with placebo.^{8–10,12,14} Two studies compared alpha blockers to anticholinergic.^{10,21} Six studies compared combination therapy with alpha blockers and anticholinergic agent to anticholinergic monotherapy.^{8–10,13,20,21} Five studies administered tamsulosin (0.2–0.4 mg orally),^{10,13,17,19,21} while the remaining six studies administered terazosin (two studies: 1–10 mg orally after titration),^{15,16} naftopidil (two studies: 25 mg orally),^{8,9} alfuzosin (one study: 10 mg orally),¹⁴ or doxozosin (one study: 4 mg orally).²⁰ Solifenacin (three studies: 5 mg orally/one study: dose not reported),^{8,13,20,21} tolterodine (two studies: 4 mg orally),^{9,19} or propiverine (one study: 30 mg orally)¹⁰ were used as anticholinergic monotherapy or combination therapy with alpha blockers.

Six studies specified funding sources: four were supported by pharmaceutical companies^{14,16,17,21} and two were funded by institution.^{17,19} Only two studies reported their conflicts of interest: one

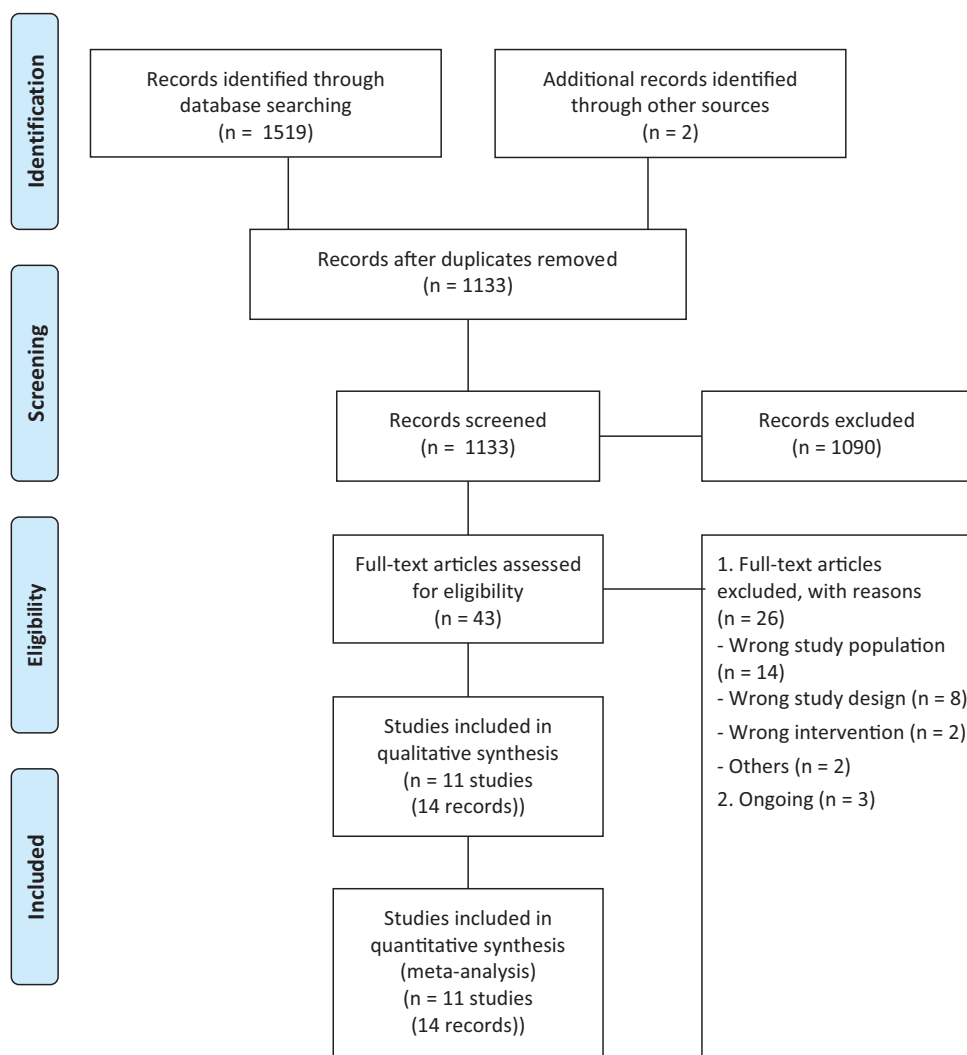


Figure 1. Flow diagram.

study reported no conflicts of interests;^{13,19} the other reported having relationships with pharmaceutical companies.¹⁶

Effect of the intervention

Alpha blocker versus placebo. We contained four studies comparing alpha blocker *versus* placebo with short-term follow-up which randomized 456 participants (alpha blockers: 231, placebo: 225) in the analysis (Table 1).^{14–17}

Urologic symptom score: Based on four studies with 407 participants in the analysis, alpha blocker likely reduces urological symptom score measured by IPSS [mean difference (MD): -1.50 , 95% confidence interval (CI): -2.91 to -0.09 ;

$I^2 = 47\%$; moderate CoE].^{14–17} We downgraded the CoE for serious study limitations (-1).

Quality of life: Based on three studies with 274 participants in the analysis, alpha blocker may improve QoL measured by IPSS-quality of life (IPSS-QoL) or American Urological Association Bother Score (standardized MD: -0.35 , 95% CI: -0.85 to 0.15 ; $I^2 = 69\%$; low CoE).^{14–16} We downgraded the CoE for serious study limitations (-1) and serious inconsistency (-1).

Adverse event: Based on three studies with 374 participants in the analysis, alpha blocker may have little to no difference in overall adverse events [risk ratio (RR): 1.09 , 95% CI: 0.55 to 2.15 ; 24 more adverse events per 1000 women

Table 1. Baseline characteristics of the included studies.

Study name	Trial period (year to year)	Setting/ country	Total no. of randomized participants	Description of participants	Alpha-blocker (n)	Comparator (n)	Age (mean, years)	Urologic symptom scores (mean, e.g. IPSS)	Qmax (mean, ml/s)	PVR (mean, ml)	Duration of intervention (duration of follow-up)
Lee <i>et al.</i> ¹⁴	NR	Multicenter/ Korea	187	Voiding symptoms for ≥3 months, AUA-SS ≥15, Qmax <15 ml/s with a voided volume of >100 ml and PVR >150 ml	Alfuzosin (97)	Placebo (90)	Alfuzosin, 57.4; placebo, 57.9	Alfuzosin, total AUA-SS = 23.0/ storage AUA-SS = 9.0/voiding AUA-SS = 15.0; Placebo, total AUA-SS = 22.0/ storage AUA-SS = 9.0/ voiding AUA-SS = 14.0	Alfuzosin, 9.9; placebo, 11.3	Alfuzosin, 24.0; placebo, 21.5	8 weeks
Lepor and Theune ¹⁵	NR	Single center/ USA	29	AUA-SS ≥8, PVR ≤300ml	Terazosin (14)	Placebo (15)	Terazosin, 60.6; placebo, 62.8	Terazosin, AUA-SS = 16.4; Placebo, AUA-SS = 12.7	Terazosin, 15.6; placebo, 19	NR	6 weeks
Low <i>et al.</i> ¹⁶	14 weeks	Multicenter/ Northern Malaysia	100	Total IPSS ≥8 for ≥1 month	Terazosin (50)	Placebo (50)	NR	Terazosin, 21.8; placebo, 21.1	Terazosin, 21.8; placebo, 21.1	Terazosin, 66.7; placebo, 57.9	14 weeks
Pummangura and Kochakarn ¹⁷	2004 to 2005	Single center/ Thailand	140	IPSS ≥8	Tamsulosin (70)	Placebo (70)	Tamsulosin, 45.3; placebo, 49.8	Tamsulosin, IPSS = 18.2; placebo, IPSS = 21.3	Tamsulosin, 18.0; placebo, 18.8	NR	4 weeks
Robinson <i>et al.</i> ¹⁹	2002	Multi center/ Europe (12 countries and 39 study sites)	364	OAB symptoms for ≥3 months	Tamsulosin (242)	Tolterodine (61) Placebo (61)	NR	NR	NR	NR	6 weeks
Yoo <i>et al.</i> ²¹	NR	Multicenter/ Korea	144	OAB symptoms, IPSS ≥8, OABSS ≥2 in Q3 with ≥3 of total OABSS and frequency ≥8/day on voiding diary	Tamsulosin + solifenacin (73)	Solifenacin (71)	NR	NR	NR	NR	12 weeks
Krhut <i>et al.</i> ¹⁰	NR	Single center/Czech Republic	28	OAB symptom for ≥3 months, frequency ≥8/day, frequency ≥24/3 days, urgency with or without urgency ≥3/3 days on voiding diary	Tamsulosin + propiverine (16)	Propiverine (12)	Tamsulosin + propiverine, 58.0; propiverine, 55.7	NR	Tamsulosin + propiverine, 29.2; propiverine, 29.2	NR	8 weeks

(Continued)

Table 1. (Continued)

Study name	Trial period (year to year)	Setting/ country	Total no. of randomized participants	Description of participants	Alpha-blocker (n)	Comparator (n)	Age (mean, years)	Urologic symptom scores (mean, e.g. IPSS)	Qmax (mean, ml/s)	PVR (mean, ml)	Duration of intervention (duration of follow-up)
Yangyun <i>et al.</i> ²⁰	2010 to 2013	Single center/ China	93	OAB symptom for ≥3 months, frequency ≥8/day, nocturia ≥2/day, each time urine <200ml on voiding diary, OABSS urgency score >2 FSFI <25	Doxazosin + solifenacin (49)	Solifenacin (44)	Doxazosin + solifenacin, 32.9; solifenacin, 33.3	NR	Doxazosin + solifenacin, 20.5; solifenacin, 19.4	Doxazosin + solifenacin, 14.4; solifenacin, 15.1	4 weeks
Huo <i>et al.</i> ⁸	NR	Single center/ China	67	OAB symptoms, OABSS urgency score >2	Naftopidil (21)	Solifenacin (22) Naftopidil + Solifenacin (24)	NR	NR	NR	NR	4 weeks
Jie <i>et al.</i> ⁹	2007 to 2008	Single center/ China	35	Urgency, frequency ≥8/day, nocturia ≥2/day, each time urine <200ml	Naftopidil + tolterodine (18)	Tolterodine (17)	37.4	NR	Naftopidil + tolterodine, 10.6; tolterodine, 11.2	NR	4 weeks
NCT01533597 ¹³	2010 to 2014	Single center/ Korea	70	OAB symptoms for ≥3 months, IPSS ≥8, OABSS ≥3 and OABSS urgency score ≥2, frequency ≥8/day, urgency ^a ≥1/day on voiding diary	Tamsulosin + solifenacin (35)	Solifenacin (35)	Tamsulosin + solifenacin, 52.3; solifenacin, 52.1	Tamsulosin + solifenacin, IPSS = 18.0; solifenacin, IPSS = 17.6	Tamsulosin + solifenacin, 19.7; solifenacin, 22.4	Tamsulosin + solifenacin, 23.2; solifenacin, 19.3	24 weeks

FSFI, female sexual function index; IPSS, International Prostate Symptom Score; NR, not reported; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score; PVR, post void residual; Qmax, maximum flow rate.
^aUrgency is defined as a level of 3–5 in a 5-point Urinary Sensation Scale.

(95% CI: 119 fewer to 305 more; $I^2 = 69\%$; low CoE)].^{14,16,17} We downgraded the CoE for serious study limitations (-1) and serious inconsistency (-1).

Acute urinary retention: We found no event for acute urinary retention in either study group.¹⁴⁻¹⁷ We downgraded the CoE for serious study limitations (-1) and very serious imprecision (-2).

Qmax: Based on four studies with 416 participants in the analysis, alpha blocker likely results in little to no difference in Qmax (MD: -0.33, 95% CI: -1.68 to 1.01; $I^2 = 1\%$; moderate CoE).¹⁴⁻¹⁷ We downgraded the CoE for serious study limitations (-1).

PVR: Based on two studies with 254 participants in the analysis, alpha blocker likely results in little to no difference in PVR (MD: -3.59, 95% CI: -19.44 to 12.25; $I^2 = 31\%$; moderate CoE).^{14,16} We downgraded the CoE for serious study limitations (-1).

Alpha blocker versus anticholinergic. We included only one study comparing alpha blocker *versus* anticholinergic with short-term follow-up which randomized 43 participants (alpha blocker 21, anticholinergic 22) in the analysis.⁸ The study reported adverse event and acute urinary retention outcome (Table 3).

Adverse event: We are very uncertain about the effect of alpha blocker on overall adverse events [RR: 0.52, 95% CI: 0.05 to 5.36; 44 fewer adverse events per 1000 women (95% CI: 86 fewer to 396 more; very low CoE)]. We downgraded the CoE for serious study limitations (-1) and very serious imprecision (-2).

Acute urinary retention: We found no event for acute urinary retention in either study group. We downgraded the CoE for serious study limitations (-1) and very serious imprecision (-2).

Combination therapy with alpha blocker and anticholinergic versus anticholinergic. We included five studies comparing alpha blocker *versus* combination therapy with short-term follow-up which randomized 380 participants (alpha blocker: 194, placebo: 186) in the analysis (Table 4).^{8,10,13,20,21}

Urologic symptom score: Based on two studies with 175 participants in the analysis, combination therapy likely results in little to no difference in

urological symptom score measured by IPSS (MD: -0.35, 95% CI: -1.98 to 1.27; $I^2 = 0\%$; moderate CoE).^{13,21} We downgraded the CoE for serious study limitations (-1).

Quality of life: Based on two studies with 175 participants in the analysis, combination therapy likely results in little to no difference in QoL measured by IPSS-QoL (MD: -0.11, 95% CI: -0.48 to 0.27; $I^2 = 0\%$; moderate CoE).^{13,21} We downgraded the CoE for serious study limitations (-1).

Adverse event: Based on three studies with 209 participants in the analysis, we are very uncertain about the effect of combination therapy on overall adverse events [RR: 1.07, 95% CI: 0.40 to 2.84; 5 more adverse events per 1000 women (95% CI: 42 fewer to 128 more; $I^2 = 0\%$; very low CoE)].^{8,13,20} We downgraded the CoE for serious study limitations (-1) and very serious imprecision (-2).

Acute urinary retention: We found no event for acute urinary retention in either study group.^{8,20} We downgraded the CoE for serious study limitations (-1) and very serious imprecision (-2).

Qmax: Based on three studies with 175 participants in the analysis, combination therapy likely results in clinically unimportant increase in Qmax (MD: 1.74, 95% CI: 0.31 to 3.18; $I^2 = 65\%$; moderate CoE).^{10,13,20} We downgraded the CoE for serious study limitations (-1).

PVR: Based on two studies with 147 participants in the analysis, combination therapy likely results in little to no difference in PVR (MD: -2.59, 95% CI: -5.63 to 0.45; $I^2 = 0\%$; moderate CoE).^{13,20} We downgraded the CoE for serious study limitations (-1).

Risk of bias

Figure 2 shows a summary of the risk of bias assessment.

Only one study was rated as low risk of selection bias.¹⁴ We rated five studies as low risk of performance bias and detection bias for subjective outcomes such as urological symptom score and QoL.^{8-10,12,14} All studies were rated as low risk of detection bias for the remaining objective outcomes. For incomplete outcome data, huge discrepancies in rating risk of bias among the

included studies according to which outcome they reported. Given that half or more review outcomes were not reported in the included studies, unclear risk of attrition bias was noted. While rating four studies as low risk of other bias,^{8,14,17,20} we did not find any study with low risk of reporting bias.

Secondary analysis

We could not perform any secondary analyses because there were no relevant data or too few data in the included studies.

Summary of findings tables

We summarized the results in summary of findings tables in accordance with GRADE methodology (Tables 2–4).

Discussion

In this systematic review, we found that the inclusion criteria of most of the trials were based only on the patient's symptoms measured by the IPSS or the Overactive Bladder Symptom Score (OABSS). Alpha blockers likely have small beneficial effects on urologic symptom scores and QoL compared to the effects of placebo; however, both alpha blocker monotherapy and combination therapy with alpha blockers and anticholinergic agents likely have no additional effects on urologic symptom scores and QoL above and beyond the effects of anticholinergic monotherapy. While alpha blocker may have little to no difference in adverse event rate compared with placebo, there was uncertainty in other comparisons. While a few studies reported data regarding Qmax and PVR after treatment, the effects of alpha blockers on these symptoms are likely trivial (clinically unimportant) in all comparisons. According to recent EAU guidelines, the use of alpha blockers such as tamsulosin in women with BOO and detrusor underactivity bladder showed with significant improvement of symptom scores from baseline, but not urodynamic parameters, and evidence for their effectiveness is limited. For this reason, they recommended to offer uroselective alpha blocker following discussion of the potential benefits and adverse events.²²

There were several limitations with regard to applicability to contemporary practice. Studies in the present meta-analysis included patients based

on symptoms using IPSS or OABSS. Therefore, majority of the patients were not FBOO. Given the diverse clinical features of FBOO and overlapping symptoms of other voiding disorders such as OAB, the population in this review may be too heterogeneous to draw conclusions. According to the EPIC study, 8% of women in the general population experienced both storage and voiding LUTS.³ Moreover, OAB can be induced by FVD or BOO.²³ Al-Zahrani and Gajewski²⁴ reported that 27% of women with refractory OAB after antimuscarinic treatment showed FBOO in a UDS. However, only one included study used urodynamic investigation in addition to patient's symptoms.⁸ In addition, there is a lack of consensus about the standard definition of functional BOO in women. These difficulties in the diagnosis of FBOO might inhibit the identification of clear indications for using alpha blockers in women with FBOO.

Our study used the same rigorous methodology as a Cochrane Review, which includes the application of the GRADE approach and its focus on patient-important outcomes such as symptom score, QoL, and adverse events. We consistently downgraded the certainty of the evidence. The most common reasons for downgrading were study limitations (issues surrounding allocation concealment, blinding of participants, personnel, and outcome assessors, and selective reporting). In addition, we frequently downgraded for imprecision due to wide CIs that crossed the assumed threshold of clinically important differences, usually in the setting of few events.^{5–7,25}

Recently, Kim *et al.*²⁶ conducted a meta-analysis of 13 studies, including 5 RCTs, and suggested the beneficial effect of alpha blocker treatment compared with the effect of placebo on LUTS. While these results are consistent with ours, we suggest that the effects of alpha blockers are likely small compared with the effect of placebo. In addition, we performed a more comprehensive search in additional databases, including trial registries and other sources of gray literature reports, and found additional comparisons to elucidate the effects of alpha blockers alone or as part of a combination therapy compared with active treatment, namely, anticholinergic therapy. Our study found that alpha blocker monotherapy and combination therapy with anticholinergic agents did not have any beneficial effect compared with that of anticholinergic

Table 2. Alpha blocker *versus* placebo.

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with alpha
Urological symptom score assessed with: IPSS (MCID: 3) Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: range 4–14 weeks	407 (4 RCTs)	⊕⊕⊕○ MODERATE ^a	–	The mean urological symptom score ranged from 7.3 to 18.7	MD 1.5 lower (2.91 lower to 0.09 lower)
Quality of life assessed with: IPSS-QoL/AUA bother score (MCID: 0.2) Scale from: 0 (best: delighted)/Not defined to 6 (worst: terrible)/Not defined Follow-up: range 6–14 weeks	274 (3 RCTs)	⊕⊕○○ LOW ^{a,b,c}	–	–	SMD 0.35 lower (0.85 lower to 0.15 higher)
Adverse event (MCID: 0.25) Follow-up: range 4–14 weeks	374 (3 RCTs)	⊕⊕○○ LOW ^{c,d,e}	RR 1.09 (0.55–2.15)	265 per 1000	24 more per 1000 (119 fewer to 305 more)
Acute urinary retention Follow-up: range 4–8 weeks	294 (2 RCTs)	⊕○○○ VERY LOW ^{d,f}	Not estimable ^g	–	–
Maximum urinary flow (MCID: 25% change of baseline) Follow-up: range 4–14 weeks	416 (4 RCTs)	⊕⊕⊕○ MODERATE ^a	–	The mean maximum urinary flow ranged from 16.46 to 24.97 ml/s	MD 0.33 ml/s lower (1.68 lower to 1.01 higher)
Post void residual (MCID: 30 ml) Follow-up: range 8–14 weeks	254 (2 RCTs)	⊕⊕⊕○ MODERATE ^d	–	The mean post void residual ranged from 31.67 to 48.79 ml	MD 3.59 ml lower (19.44 lower to 12.25 higher)

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IPSS, International Prostate Symptom Score; MCID, minimal clinically important difference; MD, mean difference; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio; SMD, standardized mean difference.

^aDowngraded by one level for study limitations: unclear or high risk of bias in one or more domains among studies.

^bDowngraded by one level for inconsistency: substantial inconsistency.

^cNot downgraded by imprecision inconsistency appears to be associated with imprecision.

^dDowngraded by one level for study limitations: unclear risk of bias in one or more domains among studies.

^eNot downgraded by inconsistency despite moderate heterogeneity: not clinically important.

^fDowngraded by two levels for imprecision: very rare event and insufficient optimal information size.

^gNo event in control group.

agent. However, it is difficult to conclude that combination therapy does not show treatment effect on FBOO due to the heterogeneous characteristics of the patient. We believe that these results are more helpful for clinicians in real practice. Interestingly, Lee *et al.*¹⁴ evaluated the efficacy of alpha blockers for the treatment of

FBOO using diagnostic criteria through UDS. They concluded that alpha blockers might not be more effective than placebo for treating FBOO and the presence or grade of BOO did not affect the results. This may be a clue to explain the effects of alpha blockers in women with LUTS.

Table 3. Alpha blockers versus anticholinergic agents.

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticholinergics	Risk difference with alpha
Adverse event (MCID: 0.25) Follow-up: 4 weeks	43 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	RR 0.52 (0.05–5.36)	91 per 1000	44 fewer per 1000 (86 fewer to 396 more)
Acute urinary retention Follow-up: 4 weeks	43 (1 RCT)	⊕○○○ VERY LOW ^{a,c}	Not estimable ^d	–	–

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MCID, minimal clinically important difference; RCT, randomized controlled trial; RR, risk ratio.

^aDowngraded by one level for study limitations: unclear risk of selection and performance bias, and high risk of reporting bias.

^bDowngraded by two levels for imprecision: wide confidence interval crosses assumed clinically important threshold.

^cDowngraded by two levels for imprecision: very rare events and insufficient optimal information size.

^dNo event in control group.

Table 4. Combination therapy versus anticholinergic agents.

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticholinergics	Risk difference with combination
Urological symptom score assessed with: IPSS (MCID: 3) Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: range 12–24 weeks	175 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	–	The mean urological symptom score ranged from 5.7 to 9.9	MD 0.35 lower (1.98 lower to 1.27 higher)
Quality of life assessed with: IPSS-QoL (MCID: 0.5) Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: range 12–24 weeks	175 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	–	The mean quality of life ranged from 1.3 to 3.1	MD 0.11 lower (0.48 lower to 0.27 higher)
Adverse event (MCID: 0.25) Follow-up: range 4–24 weeks	209 (3 RCTs)	⊕○○○ VERY LOW ^{a,b}	RR 1.07 (0.40 to 2.84)	69 per 1000	5 more per 1000 (42 fewer to 128 more)
Acute urinary retention Follow-up: mean 4 weeks	139 (2 RCTs)	⊕○○○ VERY LOW ^{a,c}	Not estimable ^d	–	–
Maximum urinary flow (MCID: 25% change of baseline) Follow-up: range 4–24 weeks	175 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,e}	–	The mean maximum urinary flow ranged from 19.61 to 29.20 ml/s	MD 1.74 ml/s higher (0.31 higher to 3.18 higher)
Post void residual (MCID: 30 ml) Follow-up: range 4–24 weeks	147 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	–	The mean post void residual ranged from 16.11 to 32.50 ml	MD 2.59 ml lower (5.63 lower to 0.45 higher)

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IPSS, International Prostate Symptom Score; MCID, minimal clinically important difference; MD, mean difference; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio.

^aDowngraded by one level for study limitations: unclear or high risk of bias in one or more domains among studies.

^bDowngraded by two levels for imprecision: wide confidence interval crosses assumed clinically important threshold.

^cDowngraded by two levels for imprecision: very rare events and insufficient optimal information size.

^dNo event in control group.

^eNot downgrade by inconsistency despite moderate heterogeneity: not clinically important.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): IPSS and QoL	Blinding of outcome assessment (detection bias): AEs, AUR, Qmax, and PVR	Incomplete outcome data (attrition bias): IPSS	Incomplete outcome data (attrition bias): QoL	Incomplete outcome data (attrition bias): AEs	Incomplete outcome data (attrition bias): AUR	Incomplete outcome data (attrition bias): Qmax	Incomplete outcome data (attrition bias): PVR	Selective reporting (reporting bias)	Other bias
Huo 2013	?	?	?	?	+	?	?	+	+	?	?	-	+
Jie 2009	?	?	?	?	+	?	?	?	?	+	+	?	-
Krhut 2009	-	?	?	?	+	?	+	?	?	+	?	?	?
Lee 2018	+	+	+	+	+	?	?	?	?	?	?	?	+
Lepor 1995	?	?	+	+	+	-	-	+	?	-	?	?	-
Low 2008	?	?	+	+	+	+	+	?	?	+	+	?	?
NCT01533597	?	?	-	-	+	-	-	+	?	-	-	?	?
Pummangura 2007	+	?	+	+	+	+	+	+	+	+	?	?	+
Robinson 2007	+	?	+	+	+	?	+	+	+	?	?	-	?
Yangyun 2014	?	?	?	?	+	?	?	+	+	+	+	?	+
Yoo 2014	?	?	?	?	+	-	?	?	?	?	?	?	?

Figure 2. Risk of bias summary.

Conclusion

Combination therapy with alpha blocker and anticholinergics likely has no additional effect on

urologic symptom scores and QoL compared with anticholinergic monotherapy, while alpha blocker monotherapy likely has beneficial effects

compared with the effect of placebo after symptom-based treatment in women. Future studies should be performed based on more specific diagnostic criteria focusing on FBOO in women, which was considered a scientific background of alpha blocker usage to elucidate the clinical effect of alpha blockers in women with LUTS.

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Author contributions

SJK contributed to conceptualization of the study. TWK contributed to data curation and formal analysis. KDC contributed to investigation. MHK contributed to methodology. HCC contributed to supervision. TWK contributed to writing—original draft. SJK contributed to writing—review and editing. All authors contributed to approval of final manuscript.

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