α_1-adrenergic receptor antagonists versus placebo for female lower urinary tract symptoms: A meta-analysis

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Abstract. The aim of the present study was to evaluate the effectiveness of α_1-adrenergic receptor antagonists (α_1ARAs) versus placebo for female patients with lower urinary tract symptoms (LUTS). A meta-analysis of randomized controlled trials was conducted. The main outcome indices used to measure the effectiveness were the total International Prostate Symptom Score (I-PSS) and maximum urinary flow rate of female patients receiving treatment for LUTS. The I-PSS quality of life (QOL) and average urinary flow rate (AFR) were also observed and analyzed. Two randomized controlled trials with a total of 213 patients were included. Meta-analysis results were as follows: Following 4 weeks of treatment, patients taking α_1ARAs presented a significant advantage over patients under placebo in terms of total I-PSS [standardized mean difference (SMD), -0.67; 95% confidence interval (CI), -0.94 to -0.39] but no difference was observed in maximum urinary flow rate (SMD, -0.05; 95% CI, -0.32 to 0.22) between the experimental and control groups. The I-PSS QOL post-treatment was lower in the α_1ARA group compared with that in the placebo group (SMD, -0.86; 95% CI, -1.32 to -0.40) according to one study, and in the other study the improvement of AFR was not significant (SMD, 0.09; 95% CI, -0.25 to 0.43). It was concluded that α_1ARAs are more effective than placebo in female patients with LUTS.

Introduction

In the same way that benign prostatic hyperplasia (BPH) is a widespread age-related pathological condition that affects men worldwide, prostatism-like symptoms in women, referred to as female lower urinary tract symptoms (LUTS), are also common, mainly including voiding ('obstructive') and filling ('irritative') symptoms, such as weak stream, hesitancy, intermittency, nocturia, daytime frequency and urgency (1). LUTS are highly prevalent in women, particularly peri-menopausal women, but they are rarely reported as they are considered to be part of the aging process and it is assumed that no effective treatment is available. LUTS increase and become more aggravating with advancing age in the majority of individuals (2-6). Voiding symptoms were observed to be more common than filling symptoms in a study of female patients with LUTS who visited a urological clinic. Furthermore, functional bladder outlet obstruction was more prevalent than detrusor underactivity in these female patients (7).

A similarly high prevalence of filling and voiding LUTS in men and women suggests that certain aspects of the underlying etiology may be identical. Adrenergic receptors (adrenoceptors, ARs) were originally categorized into αAR and βAR subgroups. However, the application of molecular biological methods in the last few years has confirmed a total of nine AR subtypes: α_{1A} (formerly named α_{1c}), α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2 and β_3 (8). The α_{1D}AR predominates in the female detrusor and spinal cord (9,10). The α_{1A}AR is expressed at significantly higher levels than other α_1AR subtypes are in the female urethra (11,12). These findings suggest that voiding and filling symptoms have a correlation with the expression of these α_1AR subtypes, and indicates that α_1-adrenoceptor antagonists (α_1ARAs) may be used as a potentially novel treatment for female patients with LUTS.

In clinical practice, however, the use of α_1ARAs to treat LUTS in women has been adopted based on limited studies, anecdotal case reports and local experience. The specific mechanism by which α_1ARAs act in the treatment of female LUTS has not been established; however, some small sample-size clinical trials have confirmed that α_1ARAs are able to significantly improve voiding and filling symptoms in female patients with LUTS (13-16).

A meta-analysis was, therefore, carried out to determine the effectiveness of α_1ARAs versus placebo for female patients with LUTS.

Materials and methods

Search strategy. Pubmed (1966-2013), Embase (1974-2013), the Cochrane Library (issue 4, 2013), the Chinese Biomedical Literature database (1978-2013), the Chinese Sci-Tech Periodical Full-Text database (1989-2013) and the Chinese

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Periodical Full-Text database (1994-2013) were searched for randomized controlled trials in which α_1ARAs, terazosin, tamsulosin, doxazosin or alfuzosin were compared with placebo in female patients with LUTS. Related references and included studies on the Internet, according to search engines such as Google™, were also searched, and a manual search was used to find key Chinese publications in associated fields. The reference lists of included studies and reviews were searched by hand and experts in the field were contacted; unpublished studies were not sought. No limits based on language were imposed.

This search strategy was used to obtain the titles and abstracts from randomized controlled trials associated with the subject matter of this review. The titles and abstracts were screened independently by two reviewers (Long Cheng and Hao-Han Wang), who discarded studies that were inapplicable. Two reviewers independently assessed the retrieved titles and abstracts of all the identified trials to confirm fulfillment of the inclusion criteria. Disagreements were resolved in consultation with Xiao-Kan Xiong. Data extraction was carried out independently by the same authors using standard data extraction forms.

Inclusion criteria. The patients were women with LUTS, aged 20 to 70 years, with a total I-PSS ≥8. Written informed consent was provided. Excluded cases were pregnancy, breastfeeding, stress incontinence, urinary tract infection, neurological diseases including diabetes mellitus with neuropathy, previous pelvic surgery or radiation, medical conditions mimicking LUTS and concomitant medications affecting the lower urinary tract.

Types of outcome measures. The main outcome measures were total I-PSS and maximum urinary flow rate (MUFR). The I-PSS quality of life (QOL) and average urinary flow rate (AFR) were also observed and analyzed.

Types of intervention. The types of intervention were α_1ARAs versus placebo.

Methodological quality assessment and level of evidence. The Cochrane collaboration tool in Review Manager, version 5.2 (Cochrane Collaboration, Copenhagen,. Denmark) was used for assessing the risk of bias in order to evaluate the methodological quality of each randomized controlled trial. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was applied to assess the level of evidence, and GRADEprofiler software, version 3.6 (Cochrane Collaboration) was used to create the evidence profile.

Statistical analysis. The data were analyzed using Stata (version 12.0; Stata Corporation, College. Station, TX, USA) and data were extracted and pooled for summary estimates. Results are expressed for continuous outcomes as weighted mean difference or standardized mean difference, and dichotomous outcomes as relative risk with 95% confidence intervals (CI). The χ^2 statistical test was used to assess heterogeneity between trials and the I^2 statistical test was used to assess the extent of inconsistency. A fixed effect model was used for calculations of summary estimates and their 95% CI, unless there was significant heterogeneity, in which case results were confirmed using a random effects statistical model. Subgroup analyses were designed to explore important clinical differences that may be expected to alter the magnitude of treatment effects.

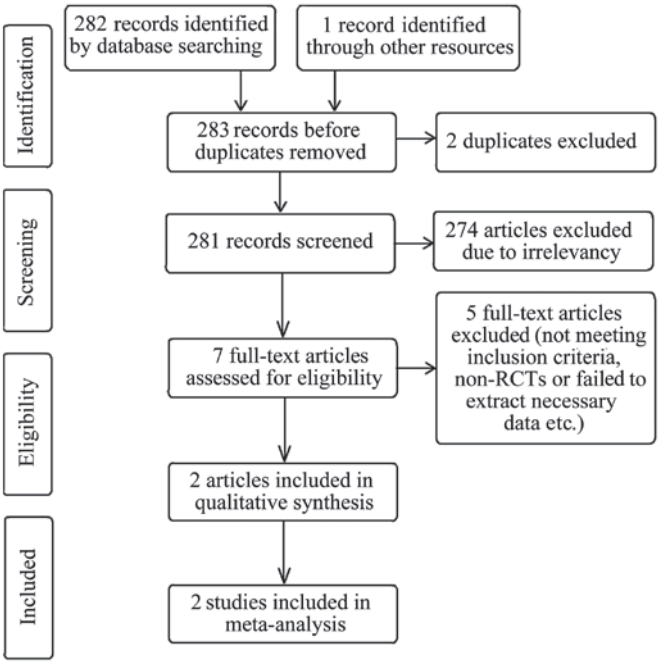

Figure 1. Flowchart for selecting randomized controlled trials (RCTs) for the meta-analysis.

Results

Search results. The selection process is depicted in Fig. 1. Seven potentially eligible trials were identified and five trials were subsequently excluded for the following reasons: Two were not controlled; one failed to extract necessary data such as the mean and standard deviations of the outcome index; one did not include a placebo group; and one was an unpublished conference article that contained no detailed data. Two randomized controlled trials totaling 213 patients [133 in the study by Pummangura *et al* (16) and 80 in the study by Low *et al* (15)] were included. The two trials reported two types of outcome including total I-PSS and MUFR. Patients were matched for age and the severity of urinary symptoms. Co-morbidities that clinically indicated symptoms similar to LUTS were not sought.

Assessing the risk of bias, and characteristics of included studies. The main characteristics of the two included studies are shown in Table I. The new 'Risk of bias' tool in Review Manager 5.2 was used to assess risk of bias (Table II).

Meta-analysis results. Results of the analysis are depicted in Fig. 2. Following almost 4 weeks of treatment, the MUFR post-treatment [standardized mean difference (SMD, -0.05; 95% CI, -0.32 to 0.22] between the experimental and control groups was found not to differ. The improvement of AFR

Table I. Characteristics of the two studies.

Study (ref.)	Gender	Age (years)	No.		Intervention		Pharmacology[b]	TI-PSS[a]			MUFR[a]			I-PSS QOL[a]			AFR[a]		
			T	C	T	C		T	C	P-value	T	C	P-value	T	C	P-value	T	C	P-value
15	Female	20-70	40	40	Terazosin	Placebo	$\alpha_{1A}=\alpha_{1B}=\alpha_{1D}$	15.6	14.38	>0.05	21.73	20.13	>0.05	4.78	5.03	>0.05		-	
16	Female	27-69	65	68	Tamsulosin	Placebo	$\alpha_{1A}=\alpha_{1D}>\alpha_{1B}$	18.2	22.50	0.001[c]	18.00	18.80	>0.05		-		7.00	7.70	>0.05

[a]Mean baseline value. [b]Effects of α1ARAs blocking three α1AR subtypes. [c]Scatter plot and Spearman's rank correlation showed that the difference in baseline TI-PSS between the two treatment groups had no significant effect on the difference in mean change from baseline in TI-PSS between groups. T, treatment group; C, controlplacebo group; MUFR, maximum urinary flow rate; TI-PSS, Total International Prostate Symptom Score; QOL, quality of life; AR, adrenergic receptor; ARA, andrenergic receptor antagonist.

Table II. Assessment of the risk of bias in the studies.

Study (ref.)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assesment	Incomplete outcome data	Selective reporting	Other bias
15	Low risk[a]	Unclear risk[a]	Low risk[b]	Low risk[c]	Low risk[d]	Low risk[e]	Low risk[f]
16	Low risk[g]	Low risk[g]	Low risk[h]	Low risk[c]	Low risk[i]	Low risk[j]	Low risk[f]

[a]Randomized controlled trial, [b]terazosin and placebo were used similarly when given to subjects, [c]double blind, [d]results of intent-to-treat analysis and per-protocol analysis are similar, [e]research plan and outcomes reported in paper, [f]no significant other bias found, [g]block randomization size of four was carried out by computer-generated random numbers, [h]study medications were packaged in a concealed card to maintain blinding in the pharmacy unit, [i]no effect of missing subjects on the trial outcome, [j]there is sufficient reason to verify that the statistically significant difference in baseline International Prostate Symptom Score between the two group (P=0.001) did not affect the trial outcome.

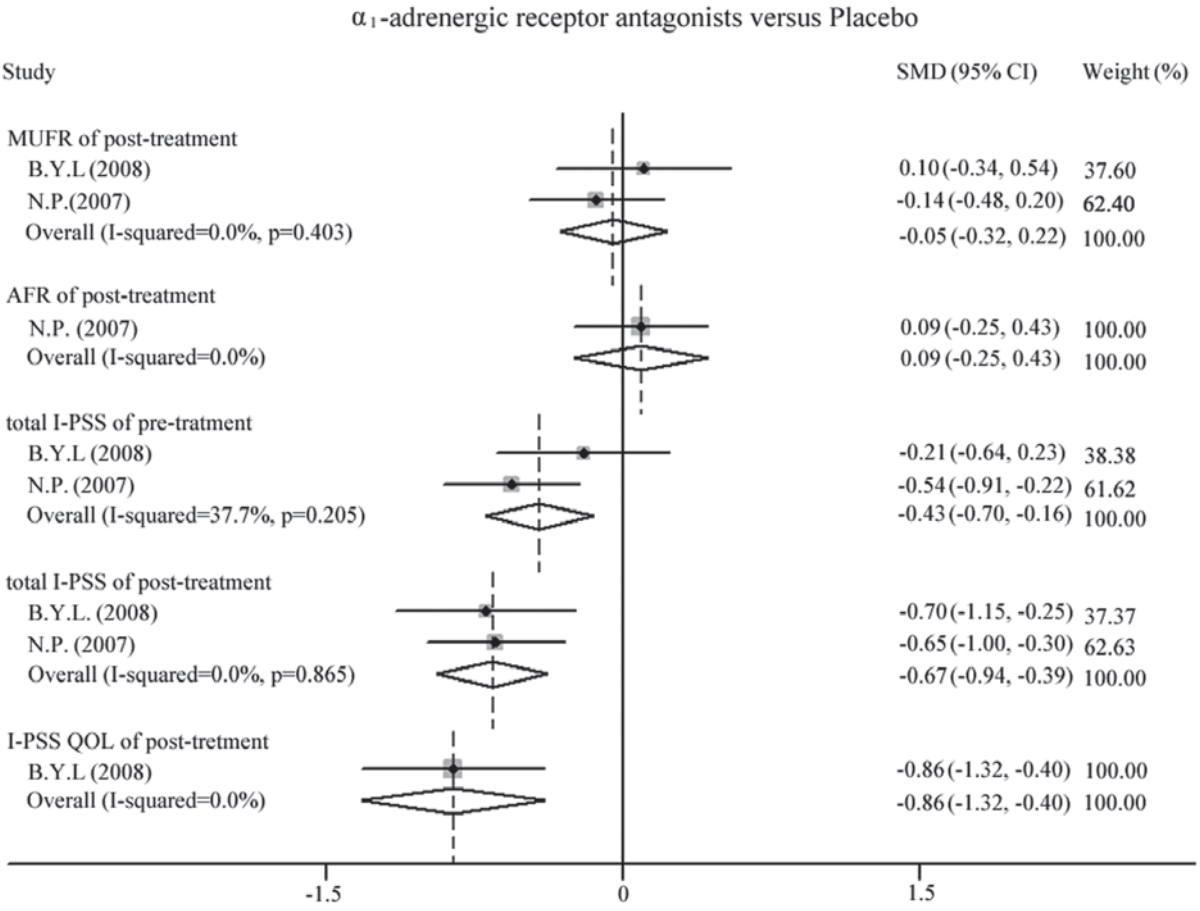

Figure 2. Forest plots for the results of the meta-analysis: α_1-adrenergic receptor antagonists versus placebo for female lower urinary tract symptoms. MUFR, maximum urinary flow rate; AFR, average urinary flow rate; I-PSS, International Prostate Symptom Score; QOL, quality of life; SMD, standardized mean difference; CI, confidence interval; B.Y.L, Low *et al* (15); N.P., Pummangura and Kochakarn (16).

was not significant (SMD, 0.09; 95% CI, -0.25 to 0.43) in the study conducted by Pummangura *et al* (16). The meta-analysis indicates that the two groups are inhomogeneous, due to a statistically significant difference (P=0.001) in the baseline I-PSS between experimental and control groups (16). In general, the total I-PSS was decreased in both groups following treatment compared with the baseline. In patients receiving α_1ARAs and placebo, the total I-PSS following treatment was lower than that prior to treatment, but the total I-PSS was significantly lower in females treated with α_1ARAs than in females treated with placebo (SMD, -0.67; 95% CI, -0.94 to -0.39). In addition, the I-PSS QOL post-treatment was lower in the α_1ARA group compared with that in the placebo-treated group (SMD, -0.86; 95% CI, -1.32 to -0.40) *(*15).

GRADE profile of evidence. The quality of evidence in the included studies, as determined by the GRADE approach, is shown in Table III. Two critical outcome measures: Total I-PSS and I-PSS QOL, and two important outcomes: MUFR and AFR, were judged to indicate high-quality evidence.

Discussion

A randomized double-blind study of 29 women in New York reported by Lepor and Theune (17) in 1995 indicated that terazosin was not effective for relieving prostatism-like symptoms. Another open non-randomized trial that used doxazosin, demonstrated that α_1ARAs were at least as effective as the anticholinergic drug hyoscyamine in reducing the total I-PSS (13). These studies were excluded due to non-conformity of the inclusion criteria. In the study by Chang *et al* (14), which comprised 97 female patients and was not placebo controlled, the outcome suggested that tamsulosin improved voiding symptoms and urodynamic parameters in nearly one-third of women with voiding difficulty, and comparable good therapeutic response rates were observed between patients with bladder outlet obstruction and detrusor underactivity (14). This disagreement among studies of whether α_1ARAs are more effective than placebo in the treatment of female LUTS was perplexing; hence, the collection and evaluation of studies concerning the efficacy of α_1ARAs in the treatment of female LUTS in the present meta-analysis was important and it may provide clinicians with a temporary guideline for selecting α_1ARA treatments.

Although the number of studies included in the present meta-analysis was small, the quality of the two studies and the reliability of the outcome measures were high. Due to the low number of participants it was not possible to reach a reliable conclusion; however, a low risk of bias and a high GRADE quality of evidence suggested that the outcome measures were reliable, at least in terms of the two included studies. The two studies mentioned randomized, double-blind, allocation

Table III. GRADE profile of evidence of the included studies.

Outcome	No. of study	Design	Quality assessment					No. of patients		Absolute effect, SMD (95% CI)	Quality	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	α_1-AR antagonists	Placebo			
TI-PSS	2	RCT	Not serious	Not serious	Not serious	Not serious	None	105	108	-0.67 (-0.94 to-0.39)	High	Critical
MUFR	2	RCT	Not serious	Not serious	Not serious	Not serious	None	105	108	-0.05 (-0.32 to 0.22)	High	Important
I-PSS QOL	1	RCT	Not serious	Not serious	Not serious	Not serious	None	40	40	-0.86 (-1.32 to -0.4)	High	Critical
AFR	1	RCT	Not serious	Not serious	Not serious	Not serious	None	65	68	0.09 (-0.25 to 0.43)	High	Important

Study 2, Low *et al* (15); Study 1, Punmangura *et al* (16); AFR, average urinary flow rate. AR, adrenergic receptor; CI, confidence interval; I-PSS, International Prostate Symptom Score MUFR, maximum urinary flow rate; QOL, quality of life; RCT, randomized controlled trial; SMD, standardized mean difference; TI-PSS, Total International Prostate Symptom Score.

concealment, and one of them included intent-analysis. The majority of participants were Asian, so any differences due to ethnicity could not be observed. In clinical trials conducted in the future, it may be appropriate to expand the sample size and select participants of different nationalities.

The bladder, bladder neck and urethra are responsible for urine storage and voiding in females. During the storage phase of the micturition cycle, the bladder relaxes to accommodate increasing volumes of urine at acceptable pressures, and the bladder neck and urethra contract to provide resistance to prevent involuntary leakage. During the micturition phase, the bladder neck and urethral muscle relax to allow the detrusor to contract and expel urine without major resistance. The α_{1D}AR predominates in the female detrusor and the α_{1A}AR is expressed at higher levels than other α_1AR subtypes in the female urethra (including the bladder neck) (9-12). Therefore, the efficacy of α_1ARAs for the treatment of female LUTS may be explained by the targeting of two possible mechanisms. The first is dysfunction of the bladder neck and urethra, causing functional outlet obstruction and secondary detrusor overactivity, which is similar to bladder outlet obstruction in men with BPH. The second possibility is increased α_1AR activity in the detrusor, causing frequency and urgency (18); however, from the meta-analysis results, only total I-PSS and I-PSS QOL improved following α_1ARA treatment with no alteration of the MUFR and AFR compared with those of the placebo groups. If α_1ARAs relax the bladder neck and urethral muscle, it is possible that MUFR and AFR could improve. More studies are required to confirm whether the difference of total I-PSS and I-PSS QOL is associated with MUFR and AFR in the control group. In terms of terazosin and tamsulosin blocking α_{1A}- and α_{1D}ARs (Table I), the bladder neck, urethral muscle and detrusor would be relaxed under the effect of these drugs. It is hypothesized that the fact that there was no clear alteration of the MUFR and AFR was as a result of the functional bladder outlet obstruction remitting and the detrusor pressure reducing over time. Highly selective α_{1A}ARAs may improve the MUFR and AFR for women with LUTS including functional bladder outlet obstruction along with possible detrusor overactivity.

In the present analysis, α_1ARAs were indicated to be more effective than placebo in reducing total I-PSS and improving QOL in females with LUTS; however, MUFR and AFR did not increase significantly and it was not clear whether the alteration of total I-PSS and IPSS QOL was associated with changes of MUFR and AFR for females with LUTS under α_1ARA treatment. As the sample size was small and the patients were from a limited geographical area, further clinical trials are required to expand the sample size and select participants of different ethnicities. More high-quality, multi-center, randomized controlled trials are required.

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