Comparison of add-on medications for persistent storage symptoms after α-blockers in BPH patients – a network meta-analysis

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Abstract

Background

Patients with benign prostatic hyperplasia (BPH) received α-blockers as first-line therapy to treat lower urinary tract symptoms (LUTS), but some individuals still experienced residual storage symptoms. Antimuscarinics, β3-agonists, and desmopressin are effective add-on medications. Nevertheless, currently there is no evidence for the appropriate choice of first add-on medication. The aim of this systematic review was to investigate the clinical benefits of antimuscarinics, β3-agonists, and desmopressin added to α-blockers for persistent storage symptoms in BPH patients.

Methods

A comprehensive literature search of randomized controlled trial (RCT) comparing the efficacy of different add-on medications for BPH patients with persistent storage symptoms despite α-blockers treatment was conducted. The clinical outcomes included the International Prostate Symptom Score (IPSS), IPSS storage sub-score, nocturia, micturition, and urgency. Network meta-analysis was performed to estimate the effect size. Surface under cumulative ranking curves (SUCRAs) were used to rank the included treatments for each outcome.

Results

A total of 15 RCTs were identified. Add-on imidafenacin or mirabegron showed significant improvement across all outcomes assessed. Other add-on medications of desmopressin, tolterodine, solifenacin, fesoterodine, and propiverine showed positive benefits for most but not all outcomes. Based on the SUCRA rankings, add-on desmopressin was related to the best ranked treatment for IPSS and nocturia, and add-on imidafenacin was the best for IPSS storage sub-score and micturition.

Conclusions

BPH patients presented with persistent storage symptoms despite α-blockers administration are recommended to received additional treatment. Desmopressin and imidafenacin may considered to be high-priority add-on treatment due to the superior efficacy than other medications.

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in elderly male population, occurring in nearly 70% of men aged > 60 years and increase with age [1]. BPH can cause lower urinary tract symptoms (BPH/LUTS) via obstruction of bladder neck, which may be bothersome and have a detrimental impact on quality of life (QoL). LUTS/BPH was found to affect 50%-75% in men aged > 50 years, increasing to 80% in men aged > 70 years [2]. For men with moderate-to-severe or bothersome LUTS/BPH, α-blockers are now prescribed as first-line pharmacological agents that target the prostate and bladder outlet.

Nonetheless, some men with LUTS/BPH fail to respond with to α-blockers, particularly among those with storage symptoms [3–5].

Overactive bladder (OAB) was a complex of storage symptoms, which was defined as urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia according to the 2022 ICS committee [6]. The coexistence of OAB and BPH (OAB/BPH) was widely identified, and storage symptoms were found to be more bothersome than voiding symptoms [7]. Although α-blockers were given as initial treatment for BPH with moderate to severe LUTS, a subset of patients still experienced persistent OAB symptoms in different severity degrees, which may be caused by urodynamic detrusor overactivity (DO) or bladder outlet obstruction (BOO) secondary to BPH [8]. The efficacy of different classes of medication added to α-blockers for OAB/BPH were identified in previous studies. Antimuscarinics was suggested to be added if BPH patients with moderate-to-severe BPH still have residual storage symptoms suggestive of OAB after α-blockers administration based on the 2018 European Association of Urology Guideline [9]. β3-agonists such as mirabegron was found to be effective as an add-on treatment for OAB symptoms caused by BPH following α-blockers treatment. [10–12] Desmopressin, an antidiuretic agent, was confirmed to be an active therapy by adding to α-blockers in reducing the International Prostate Symptom Score (IPSS) and nocturia episodes for patients not satisfied with α-blockers monotherapy with persistent nocturia [13, 14].

As far as we know, a number of medications in different classes were available for adding to α-blockers for BPH patients with residual OAB symptoms with variable efficacy and safety outcome. However, evidence supporting the suitable choice of a second-line add-on agent is currently uncertain. Therefore, we conducted a systematic review and network meta-analysis to investigate the clinical benefit of add-on antimuscarinics, β3-agonists, and desmopressin for BPH patients with residual OAB symptom after α-blockers administration.

Materials and Methods

Search strategy

An electronic search of MEDLINE and EMBASE databases from inception to 2021, was conducted to identify all eligible studies. The search strategy involving the following keywords (MeSH terms and free text words): “benign prostatic hyperplasia,” “overactive bladder,” “α-blockers,” “add-on therapy,” “randomized controlled trial,” and “clinical trial.” Only full-text articles published in English were included. The ongoing trials were located by searching the Cochrane Controlled Trials Register. To identify additional studies, reference lists of the included studies were examined.

Study Selection

Trials were eligible for inclusion if they were parallel-design RCTs or cross-over studies; included patients diagnosed with BPH receiving α-blockers as initial treatment for at least 4 weeks; compared any of the following drugs added to α-blockers: desmopressin, imidafenacin, tolterodine, mirabegron, solifenacin,

fesoterodine, propiverine. The outcome for this study was the IPSS, IPSS storage sub-score, nocturia, micturition, and urgency. Trials that included one or more of these outcomes were considered eligible. Duplication was initially removed using a reference management software, and two authors then independently assessed the eligibility of remaining studies by reviewing the titles, abstracts, and full articles sequentially.

Data Extraction and Quality Assessment

Two investigators independently extracted the data by using a standardized form. The following data were extracted: study information (ie, title, authors, country, publication time, patient number, and treatment duration), patient characteristics (i.e. age, race, bladder diary information, prostate volume, prostate specific antigen, post-void residual volume (PVR), maximum urinary flow (Q_{max})), intervention, control, and outcomes (i.e. estimated effects, standard deviation, standard error, P-value, and/or confidence interval [CI]). Quality assessment was performed by using the risk of bias (ROB) assessment tool which was suggested by the Cochrane Handbook for Systematic Reviews of Interventions. [15] Any discrepancy was resolved by discussion between the two reviewers or a third reviewer.

Results

Literature search

A total of 759 studies were imported on a comprehensive literature search. Among these studies, 8 duplicates were excluded. After reviewing the titles and abstracts for screening of 751 studies, 679 of them were removed owing to irrelevance, resulting to 72 studies for a full text review. At the end of the process, 15 studies met our review inclusion criteria and remained for qualitative synthesis and quantitative meta-analysis, including 4875 patients receiving 7 different drug therapies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented in Fig. 1.

Study characteristics and Quality Evaluation

The 15 included studies were totally RCTs lasting for 6–12 weeks, with detailed clinical characteristics described in Table 1. All subjects in the 15 RCTs underwent α-blockers before randomization and were continued over the trials. For most parallel 2-arm RCTs, the effects between drugs of different classes plus α-blockers and α-blockers alone was compared, and the other 3-arm RCTs (three studies) testing different doses of the same add-on drug. The add-on treatment identified were desmopressin 0.2 mg (desmopressin + α-blockers), tolterodine 4mg (tolterodine + α-blockers), mirabegron 50 mg (mirabegron + α-blockers), solifenacin 5 and 10 mg (solifenacin + α-blockers), fesoterodine 4 mg (fesoterodine + α-blockers), propiverine 10 and 20 mg (propiverine + α-blockers), imidafenacin 0.1 and 0.2 mg (imidafenacin + α-blockers). In the study of Kaplan et al. 2020, the patients received dose titration of mirabegron (titrated from 25 to 50 mg for the last 8 weeks). Further, patients randomized into the fesoterodine arm in the study of Kaplan et al. 2012 commenced fesoterodine with optional dose

escalation (from 4 to 8 mg) at week 4 and reduction back to 4 mg at week 8. All subjects of eligible trials were males with the mean age of 66.79.

Network meta-analysis

To assess indirect treatment comparisons, a network meta-analysis was performed. The network constructions for different outcome of IPSS, IPSS storage sub-score, nocturia, micturition, and urgency were shown in Fig. 2. For all clinically assessed outcomes, 8 interventions were included in the network analysis, such as α-blockers alone, antimuscarinics + α-blockers (tolterodine + α-blockers, solifenacin + α-blockers, fesoterodine + α-blockers, propiverine + α-blockers, and imidafenacin + α-blockers), beta-3 agonists (mirabegron + α-blockers), desmopressin + α-blockers. The pairwise comparison for the treatment effect, SUCRAs, and probability of being best (Prbest) treatment were revealed in Figs. 3 and 4, respectively.

IPSS score

On the basis of 15 studies, results of IPSS analysis was presented in Fig. 2a. Propiverine was not included in this analysis from the original study. Compared to that of the α-blockers, add-on treatment with desmopressin, mirabegron, imidafenacin, tolterodine, fesoterodine was effective in reducing the total IPSS score. (Fig. 3a) However, adding solifenacin on α-blockers showed no significant improvement (mean difference: 0.00 [95% CI: -0.06, 0.06] Fig. 3a) According to the SUCRA results and Prbest score, desmopressin on α-blockers was the highest ranked treatment for the total IPSS score (SUCRA = 100%; Prbest = 100% Fig. 4a), followed by mirabegron (SUCRA = 69%), imidafenacin (SUCRA = 58.3%), tolterodine (SUCRA = 57.1%), fesoterodine (SUCRA = 48.9%).

IPSS storage sub-score

Further analysis of the IPSS storage sub-score was also conducted based on 7 studies (Fig. 2b). Among the 6 add-on treatment, imidafenacin, desmopressin, mirabegron, solifenacin, and fesoterodine effectively reduced the IPSS storage sub-score compared to that of the α-blockers. (Fig. 3b) No significant difference was found between adding tolterodine on α-blockers and α-blockers monotherapy (mean difference: 0.17 [95% CI: -0.24, 0.57] Fig. 3b). According to the SUCRA results and Prbest score, imidafenacin on α-blockers best reduce the IPSS storage sub-score (SUCRA = 93.2%; Prbest = 59.3% Fig. 4b), followed by desmopressin (SUCRA = 84.6%), mirabegron (SUCRA = 68.8%), solifenacin (SUCRA = 49.8%), fesoterodine (SUCRA = 35.6%), α-blockers (SUCRA = 13.7%), tolterodine (SUCRA = 4.3%).

Nocturia

The nocturia analysis was based on 6 studies, and the network construction was presented in Fig. 2c. In the original study, tolterodine, mirabegron, fesoterodine, and propiverine were not included for this analysis. Compared to that of the α-blockers, desmopressin, imidafenacin, solifenacin, and mirabegron were all effective as add-on treatment to reduce nocturia episodes. (Fig. 3c) According to the SUCRA results and Prbest score, desmopressin may considered to be the most successful second-line regimen

Table 1 Characteristics of the included studies

Study	Year	Study design	Initial treatment duration	Treatment arm	Patient number	Add-on intervention duration
Alquraishi et al.	2020	2-arm RCT	10 wk	*1.* α-blocker	22	
				2. α-blocker + Desmopressin	29	4 wk
Chapple et al.	2009	2-arm RCT	4 wk	*1.* α-blocker	323	
				2. α-blocker + Tolterodine	329	12 wk
Ichihara et al.	2015	2-arm RCT	8 wk	*1.* α-blocker	38	
				2. α-blocker + Mirabegron	38	8 wk
Kakizaki et al.	2019	2-arm RCT	4 wk	*1.* α-blocker	283	
				2. α-blocker + Mirabegron	282	12 wk
Kaplan et al.	2020	2-arm RCT	4 wk	*1.* α-blocker	339	
				2. α-blocker + Mirabegron	337	12 wk
Kaplan et al.	2009	2-arm RCT	4 wk	*1.* α-blocker	195	
				2. α-blocker + Solifenacin	202	12 wk
Kaplan et al.	2012	2-arm RCT	6 wk	*1.* α-blocker	472	
				2. α-blocker + Fesoterodine	471	12 wk
Kim et al.	2017	2-arm RCT	8 wk	*1.* α-blocker	39	
				2. α-blocker + Desmopressin	47	8 wk
Konstantinidis et al.	2013	2-arm RCT	1 wk	*1.* α-blocker	23	
				2. α-blocker + Fesoterodine	24	4 wk
Kwon et al.	2020	2-arm RCT	8 wk	*1.* α-blocker	19	
				2. α-blocker + Mirabegron	39	8 wk
Nishizawa et al.	2011	3-arm RCT	8 wk	*1.* α-blocker	60	

				2. α-blocker + Propiverine (10 mg) 3. α-blocker + Propiverine (20 mg)	60 62	12 wk
Takeda et al.	2013	2-arm RCT	8 wk	*1.* α-blocker *2.* α-blocker + Imidafenacin	154 154	12 wk
Yamaguchi et al.	2011	3-arm RCT	6 wk	*1.* α-blocker *2.* α-blocker + Solifenacin (2.5 mg) 3. α-blocker + Solifenacin (5 mg)	212 210 203	12 wk
Yang et al.	2007	2-arm RCT	1 wk	*1.* α-blocker *2.* α-blocker + Tolterodine	36 33	6 wk
Yokoyama et al.	2015	3-arm RCT	4 wk	*1.* α-blocker *2.* α-blocker + Imidafencin (0.2 mg) 3. α-blocker + Imidafencin (0.1 mg)	46 43 41	8 wk

for nocturia (SUCRA = 100%; Prbest = 99.9% Fig. 4c), followed by imidafenacin (SUCRA = 74.9%), solifenacin (SUCRA = 50%), and mirabegron (SUCRA = 25%).

Micturition

The micturition frequency analysis was based on 7 studies, and the network construction was presented in Fig. 2d. Desmopressin was not included in this analysis from the original study. Compared to that of the α-blockers, add-on treatment with imidafenacin, solifenacin, tolterodine, mirabegron, and fesoterodine was effective in reducing micturition. However, adding propiverine to α-blockers showed no significant improvement (mean difference: -0.38 [95% CI: -1.23, 0.47] Fig. 3d). According to the SUCRA results and Prbest score, imidafenacin on α-blockers was the highest ranked treatment for micturition (SUCRA = 98.3%; Prbest = 94.4% Fig. 4d), followed by solifenacin (SUCRA = 81.4%), tolterodine (SUCRA = 59.2%), mirabegron (SUCRA = 45.5%), propiverine (SUCRA = 35.3%), and fesoterodine (SUCRA = 27.3%).

Urgency

The analysis of urgency was based on 8 studies, and the network construction was presented in Fig. 2e. In the original study, desmopressin and propiverine were not included for this analysis. All of the add-on treatment with tolterodine, imidafenacin, solifenacin, fesoterodine, and mirabegron were more effective

than α-blockers monotherapy in reducing urgency episodes. (Fig. 3e) According to the SUCRA results and Prbest score, the probability of tolterodine on α-blockers was related to the best ranking for urgency (SUCRA = 92.2%; Prbest = 60.9% Fig. 4e), followed by imidafenacin (SUCRA = 85.6%), solifenacin (SUCRA = 56.8%), fesoterodine (SUCRA = 34.9%), and mirabegron (SUCRA = 30%).

Discussion

Although α-blockers remains to be the first-line treatment for male with BPH, there are a subset of patients still having residue OAB symptoms, including urinary urgency, urge incontinence, frequency, and nocturia. OAB symptoms caused by consistent DO may be a possible reason for treatment failure, because DO was poorly associated with BOO affected by α-blockers. Thus, there is an increasing concern in add-on treatment of OAB symptoms in patients with BPH. The add-on treatment lead to a significant improvement in patients with BPH and concomitant OAB in the total IPSS, IPSS storage sub-score, IPSS voiding sub-score, mean number of micturition per day, urgency episodes per day, nocturia episodes per day, total Overactive Bladder Symptom Score (OABSS), and mean volume voided (MVV). In general, add-on treatment appeared superior to mono-treatment in many aspects. Despite adding a second medication to α-blockers may surely be helpful in patients experiencing residue OAB, evidence of comparative effectiveness of different add-on medications may be limited in the absence of published head-to-head trial. To compare multiple add-on treatments, a network meta-analysis was developed by using both direct comparisons of interventions among trials and indirect comparisons across RCTs. [16, 17] Hence, this systematic review and network meta-analysis has assessed the efficacy of a range of medications for treating OAB on clinical outcomes as add-on treatment for patients with BPH and residual OAB symptoms despite α-blockers prescription. We have included a total of 15 RCTs containing 7 add-on medications used in 4875 patients. Our results indicated that add-on treatment appeared more effective than α-blockers alone in improving total IPSS score, IPSS storage sub-score, the mean number of micturition per day, urgency episodes per day, and nocturia episodes per day.

Patients with BPH and refractory nocturia usually do not completely respond to α-blockers, because relief of bladder outlet obstruction is not sufficient to overcome nocturia. The reason may be because the multifactorial mechanism of nocturia in aging male [18]. Nocturnal polyuria (NP), which was defined as the voided urine volume during the hours of sleep exceeded 33% of the 24 hours output, was found to be the main etiology leading to nocturia. NP is a common condition in patients having nocturia (up to 82.9%) [18], and was found to be more prevalent in elderly population due to nocturnal urine production increases with aging. Yoong et al reported that 85% of male patients with nocturia and LUTS having poor response to α-blocker were identified to have NP [19]. NP should be considered as a possible cause of refractory nocturia despite α-blocker treatment.

In our analysis, we found that desmopressin adding to α-blockers had the greatest improvement in the total IPSS score and nocturia, and ranked second in improving the IPSS storage sub-score based on the SUCRA. Desmopressin, an arginine vasopressin synthetic analogue, causes similar inhibitory effects on diuresis. It can significantly decreased nocturnal urine output and the number of nocturia episodes [20],

which may cause an subsequent improvement in storage symptoms and voiding symptoms resulting in decreased IPSS scores. A systematic review concluded that oral desmopressin added to α-blockers was more effective for improving the IPSS and nocturnal symptoms than using α-blockers alone, with a 64.3% reduction in frequency of nocturia in comparison with 44.6% [21]. Shin et al. reported a significant decrease in nocturnal urine volume, nocturia episodes, overactive bladder symptom score, urgency episodes,, and nocturnal bladder capacity index when using desmopressin plus α-blockers [22]. Bae et.al showed that mean number of nocturnal voids, total IPSS, and IPSS storage sub-score significantly improved after desmopressin add-on therapy [14]. In addition, add-on desmopressin could improve quality of life (QoL), with higher satisfaction with medication and more willing to continue the treatment for men with BPH [23]. As for the safety assessment, the most concerning adverse events of the add-on therapy with desmopressin was hyponatremia. Despite most patients who developed hyponatremia were asymptomatic, regular assessment of serum sodium after starting desmopressin add-on therapy is recommend, especially for men with advanced age. Owing to the clinical effectiveness and relative safety of desmopressin, the addition of desmopressin to α-blockers may be a suitable therapy for BPH patient with residue OAB symptoms, especially for nocturia.

While studies have shown that the addition of antimuscarinics to α-blockers was recommended for persistent OAB symptoms associated with BPH [24], comparisons among antimuscarinics were currently unclear. Based on our results, imidafenacin adding to α-blockers make greatest reduction in the IPSS storage sub-score and micturition, and also presented as a second best choice in improving nocturia and urgency based on the SUCRA. The Good-Night study showed that add-on imidafenacin caused a significant reduction in frequencies of 24-h and nocturnal micturition, and significantly reduced nocturnal urine volume in imidafenacin nightly group (α1-blocker plus 0.1 mg imidafenacin nightly) [25]. Similarly, the ADDITION study reported that add-on imidafenacin (tamsulosin 0.2 mg/d + imidafenacin 0.1 mg twice per day) resulted in significant improvements in frequencies of daytime urination, night-time urination, urinary urgency, IPSS, and total OABSS. A recent meta-analysis also concluded that adding imidafenacin to α-blockers significantly improve OAB symptoms, with a greater reduction in OABSS compared with alpha-blocker monotherapy [26]. Imidafenacin, as a antimuscarinic agent, has high affinities to the M3 and M1 muscarinic receptor subtypes and a low affinity to M2 receptors [27]. Meantime, in clinical experiments, imidafenacin also has an inhibitory effect on the contractions of detrusor smooth muscles by blocking both the postjunctional M3 receptors and the prejunctional M1 receptors in humans [28]. The reasons of superior efficacy of add-on imidafenacin over other antimuscarinics for treating OAB symptoms may be explained by its unique pharmacological effect. Imidafenacin featured by shorter half-life (2.9 hours), relatively greater selectivity and longer duration of receptor binding in the bladder than in the salivary gland and other organs in rats (6–9 hours in the bladder, 1–3 hours in the submaxillary gland; no observation in the brain) [29, 30] compared with other antimuscarinic agents. Interestingly, our results also revealed that add-on imidafenacin has greatest improvement in nocturia than other antimuscarinics. This finding was consistent with previous studies, which speculated that imidafenacin may reduce the number of nighttime voids, increase bladder capacity and improve sleep disorders [25, 31]. In an animal experiment, Watanabe et.al showed that imidafenacin

decreased urine volume by suppressing the C-fibers in the rat bladder [32]. The possible mechanism for how imidafenacin improving nocturia is that it decreases the nocturnal urine volume by the inhibition of bladder afferent nerves, causing subsequent improvement in nocturia and sleep disturbance [25]. In terms of safety, imidafenacin has fewer adverse events such as dry mouth and constipation than other antimuscarinic agents [33, 34], which could be explained because it was higher selective to the bladder. Furthermore, Wu et.al reported that imidafenacin was associated with a statistically lower withdrawal rate related to adverse events [34]. There have been concerns that antimuscarinic add-on may theoretically aggravate voiding symptoms by inhibiting detrusor muscle contraction, resulting in reducing Q_{max} improvements, increased PVR, and, in particular, cause of acute urinary retention. However, there were no significant differences with respect to the Q_{max} or the PVR after adding imidafenacin to α-blockers [26, 35]. Collectively, imidafenacin add-on treatment was effective, safe, and well-tolerated for residual OAB symptoms in patients with BPH already receiving α-blockers, with the superior efficacy on micturition, urgency, and nocturia than other antimuscarinic agents.

Our results indicated that add-on mirabegron was effective in treating residual OAB symptoms such as micturition, urgency, and nocturia in patients already receiving α-blockers, ranking second in improving IPSS score and third in IPSS storage sub-score based on the SUCRA. Previous works have corroborated our findings. Two RCTs have reported that adding mirabegron to tamsulosin showed significant improvement in total IPSS, IPSS storage sub-score, and total OABSS [12, 36]. Kaplan et al. described that adding mirabegron to tamsulosin had significant improvements in micturition, urgency, and Total Urgency and Frequency Score [11]. A recent meta-analysis showed that add-on mirabegron therapy significantly reduce the mean number of micturition, urgency episodes per day, and total OABSS compared with tamsulosin monotherapy [10]. Mirabegron was also proved to be urodynamically efficacious and safe in treating men with BPH and OAB. Add-on mirabegron treatment significantly increased Q_{max} and voided volume [37, 38]. This finding could possibly be interpreted by the pharmacology characteristics of mirabegron. Mirabegron, as a β3-agonist, not only promoted relaxation of detrusor smooth muscle to increases bladder capacity [39], but also showed competitive antagonist activity on the α_1-adrenoceptors in the urethra, resulting in urethral smooth muscle relaxation [40]. As for the safety assessment, the incidence rate of treatment-emergent adverse event (TEAE) of the adding mirabegron to α-blockers and α-blockers were similar, and TEAEs were mild in severity [10, 41]. Although increase in PVR was observed for add-on mirabegron treatment in some studies, the change of PVR was not clinically meaningful [41]. Mirabegron appeared to be a safe treatment option for patients with predominant co-existing OAB and BPH after receiving α-blockers. Furthermore, patient receiving mirabegron have significantly higher persistence and adherence rates than those treating with antimuscarinics, with lower occurrence of TEAEs including dry mouth and constipation [42, 43]. Because add-on mirabegron treatment exhibited satisfactory efficacy and safety with well-tolerance, it could be an alternative choice for residual OAB symptoms in patients not satisfied with other add-on medications with BPH having previous treatment of α-blockers.

Limitation

Based on our knowledge, this is the first network meta-analysis comparing the efficacy of different medications as an add-on treatment to α-blockers in patients with BPH and concomitant OAB. However, this study has some limitations. First, the results of our study were short-term outcomes, with duration of add-on interventions not beyond 12 weeks. Further high-quality RCTs are required to determine long-term efficacy and persistence of these add-on medications. Second, safety outcomes were not included in our study, so potential risk for adverse events still exist. Third, various types of α-blockers were included in our analysis, which may affect the results due to different α1-adrenergic receptors subtype selectivity of α-blockers. However, our primary concern was to examine the additional benefits of add-on medications. Furthermore, not all of the RCTs included in the present study evaluate a full range of urodynamic parameters, while urodynamic examination may provide important information related to bladder and urethral dysfunction.

Conclusions

Our network meta-analyses showed that BPH patients presented with persistent storage symptoms despite α-blockers administration are recommended to received additional treatment. Desmopressin and imidafenacin may considered to be high-priority add-on treatment due to the superior efficacy than other medications. Further randomized control trials are needed to evaluate long-term outcomes.

Abbreviations

BPH benign prostatic hyperplasia

LUTS lower urinary tract symptoms

RCT randomized controlled trial

IPSS International Prostate Symptom Score

SUCRA Surface under cumulative ranking curve

QoL quality of life

OAB overactive bladder

DO detrusor overactivity

BOO bladder outlet obstruction

PVR post-void residual volume

Q_{max} maximum urinary flow

CI confidence interval

ROB risk of bias

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Prbest probability of being best

OABSS Overactive Bladder Symptom Score

MVV mean volume voided

NP nocturnal polyuria

TEAE treatment-emergent adverse event

Declarations

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Author contributions

YT Su: protocol development, data collection, data analysis, manuscript writing. HL Chen: protocol development, data collection, data analysis. JYC Teoh: protocol development, data interpretation. VWS Chan: systematic review, data analysis. WJ Wu: protocol development, data interpretation. HY Lee: protocol development, data interpretation, manuscript editing.

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Availability of data and materials

The data supporting the findings of this article are available from the corresponding author on reasonable request

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

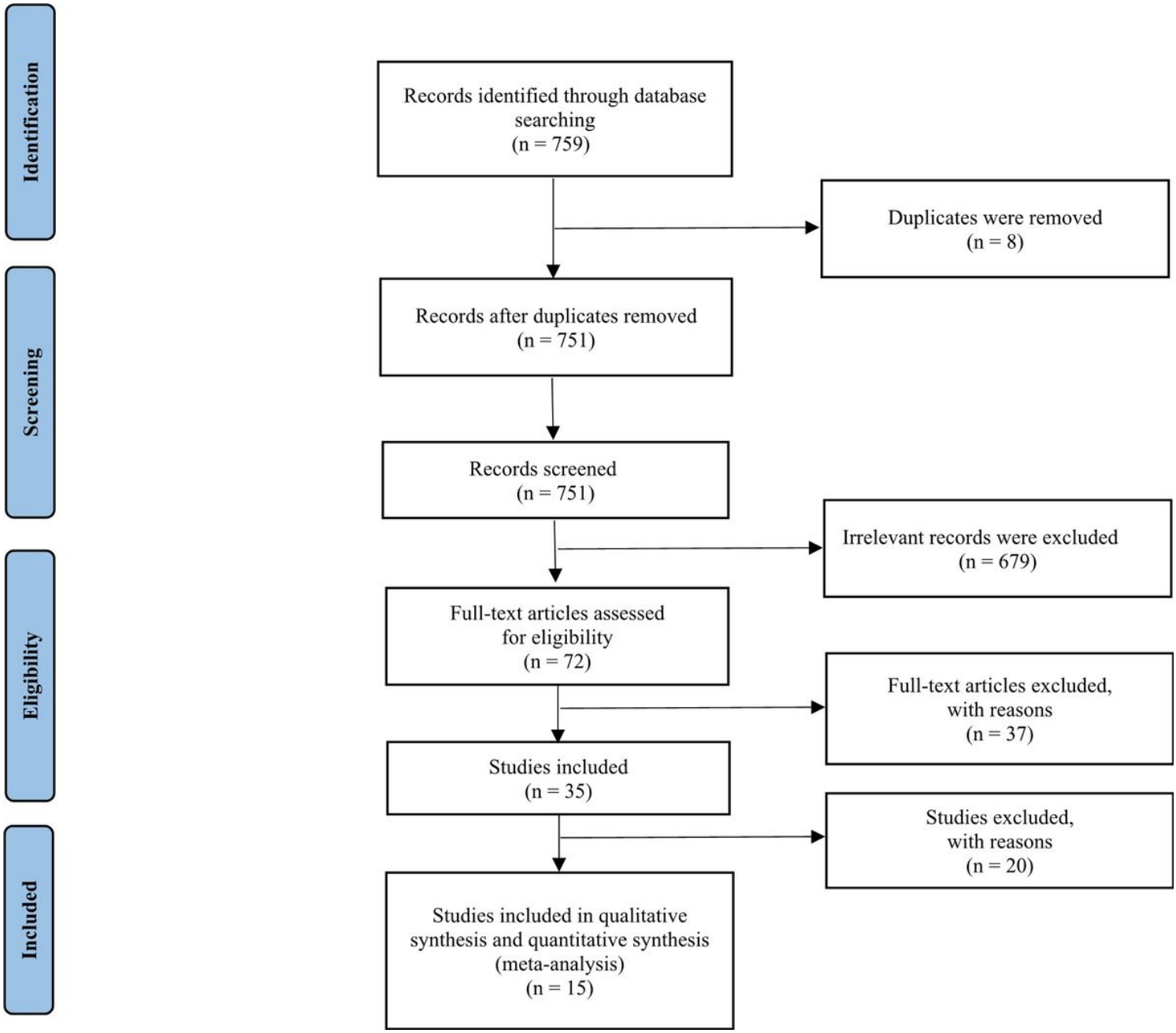

Figure 1

PRISMA flow diagram

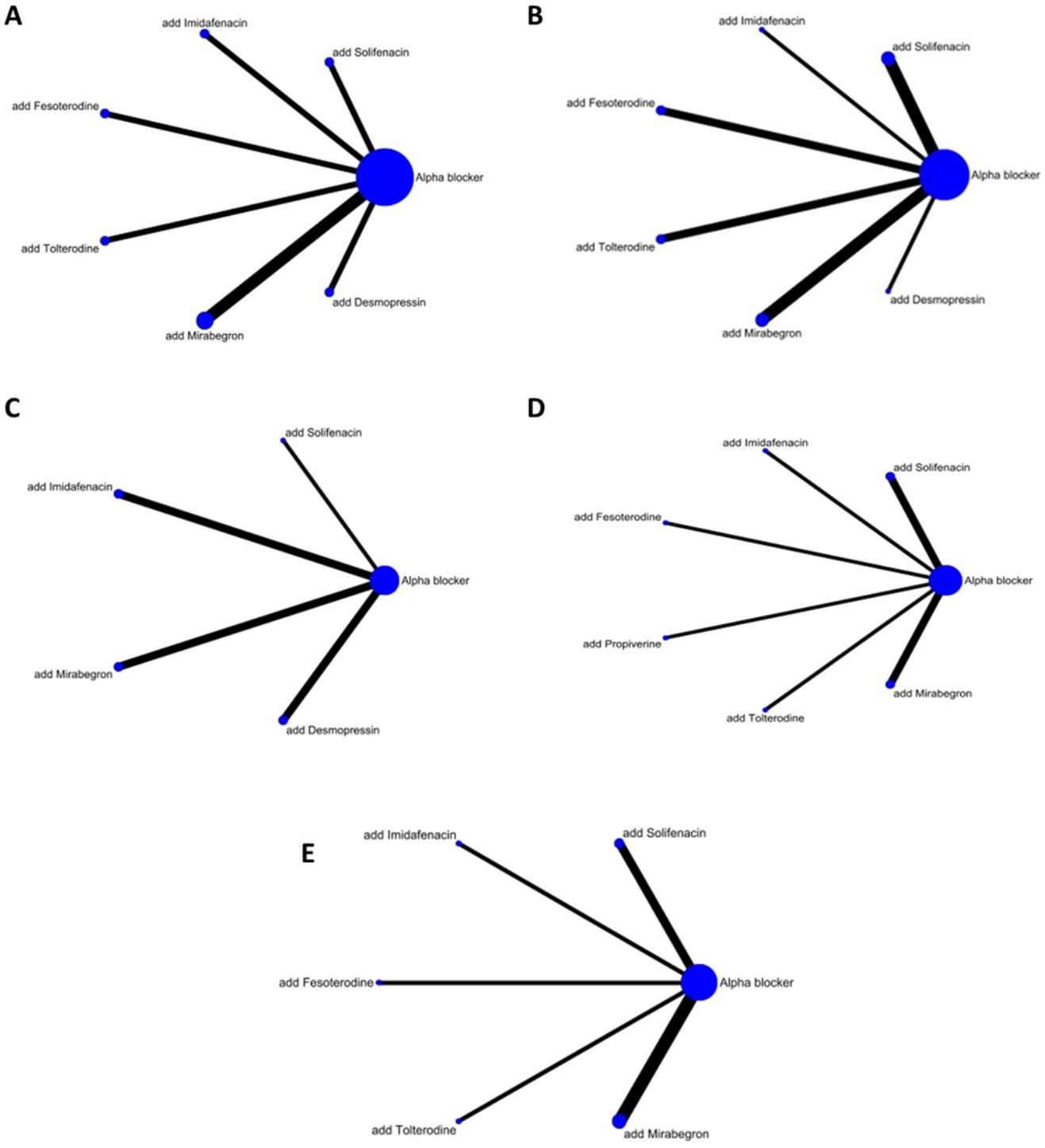

Figure 2

Network constructions for comparison in IPSS total score, IPSS storage sub-score, nocturia, micturition, and urgency (a) IPSS total score (b) IPSS storage sub-score (c) Nocturia (d) Micturition (e) Urgency

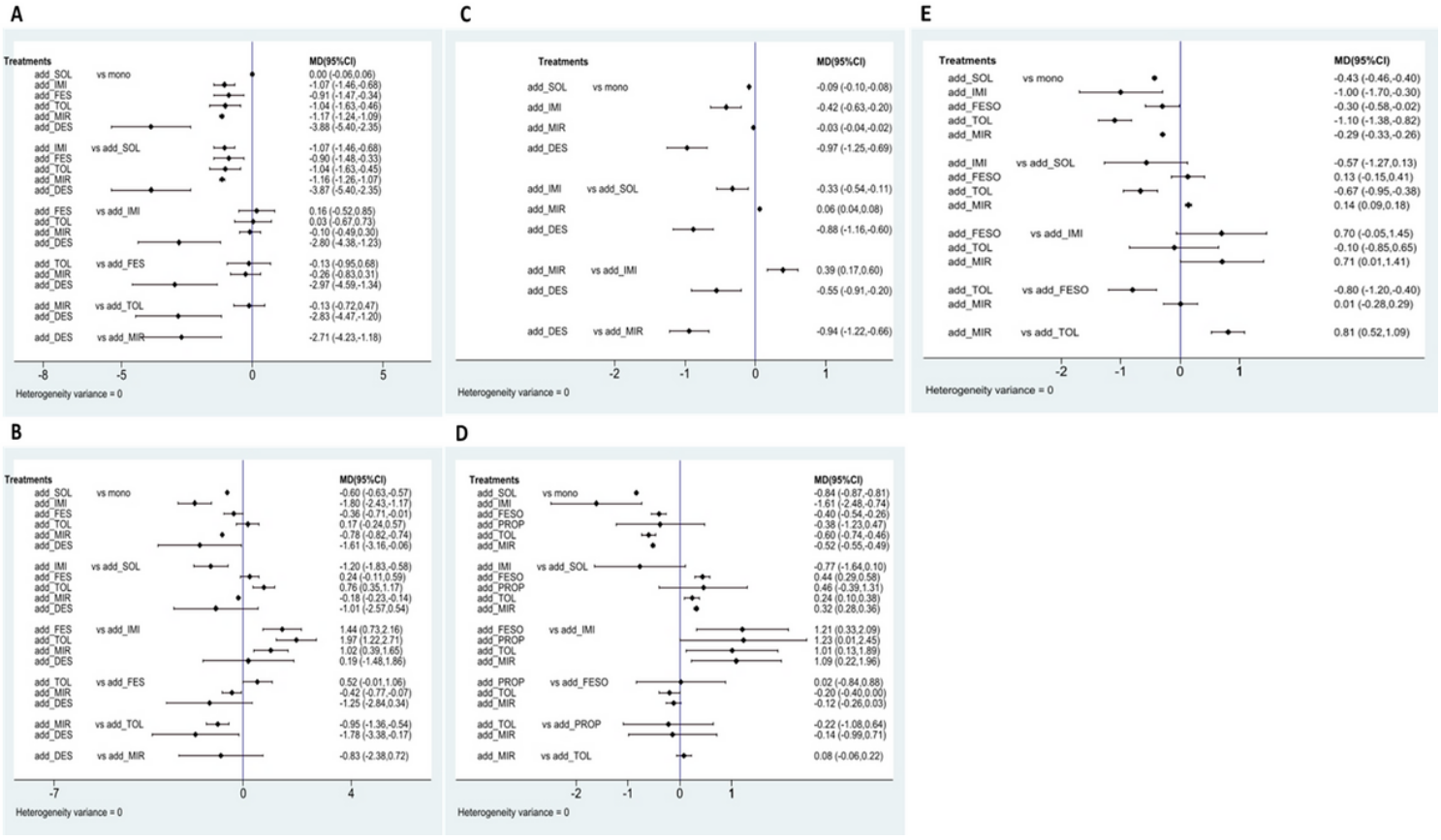

Figure 3

Summary of effect size for pairwise comparison (a) IPSS total score (b) IPSS storage sub-score (c) Nocturia (d) Micturition (e) Urgency

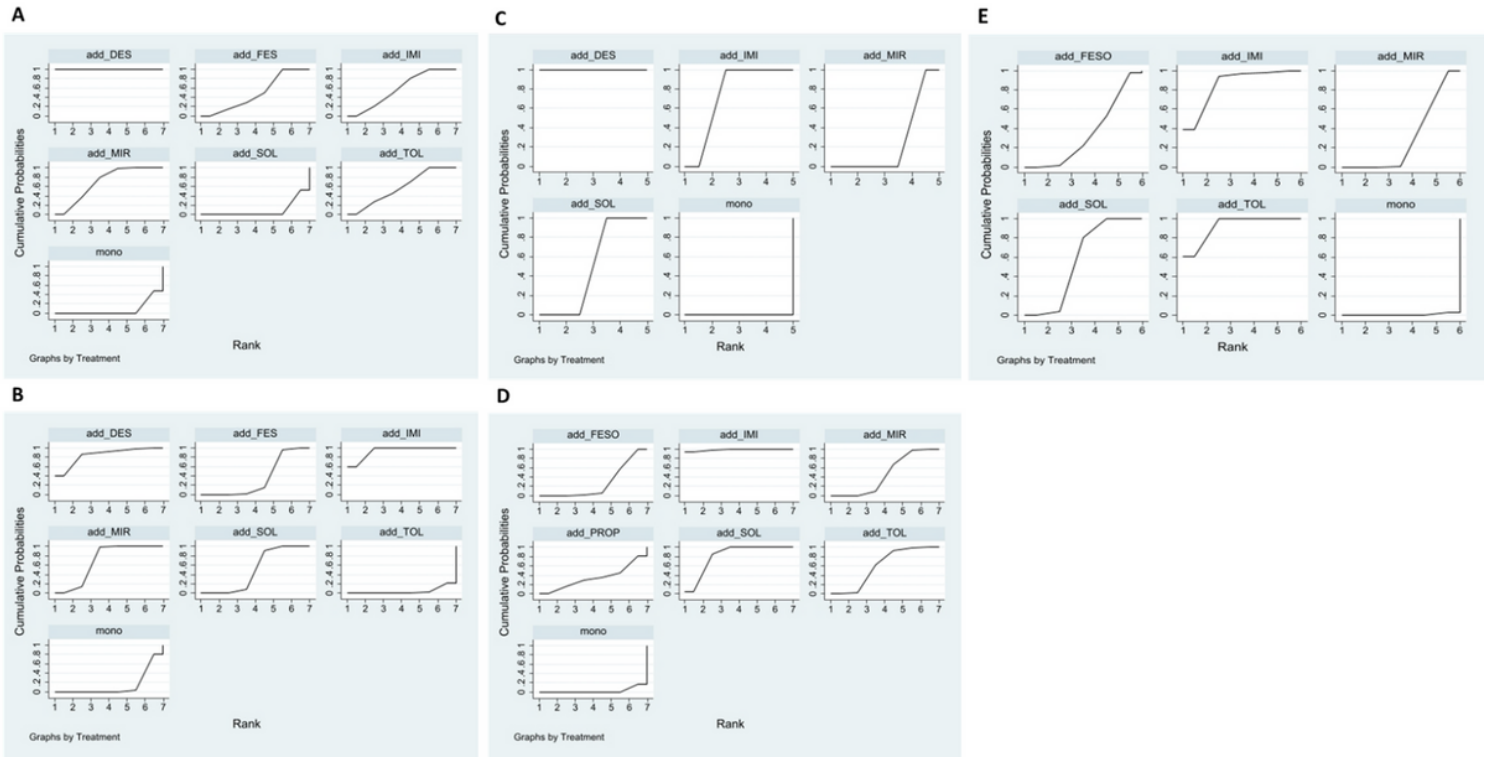

Figure 4

Cumulative ranking probability for different add-on medications (a) IPSS total score (b) IPSS storage sub-score (c) Nocturia (d) Micturition (e) Urgency