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Review – Incontinence – Editor's Choice

Systematic Review of Combination Drug Therapy for Non-neurogenic Lower Urinary Tract Symptoms

Maurizio Serati[a,*], *Karl-Erik Andersson*[b,c], *Roger Dmochowski*[d], *Enrico Finazzi Agrò*[e], *John Heesakkers*[f], *Valerio Iacovelli*[e], *Giacomo Novara*[g], *Vik Khullar*[h], *Christopher Chapple*[i]

[a] *Department of Obstetrics and Gynecology, University of Insubria, Varese, Italy;* [b] *Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston Salem, NC, USA;* [c] *Institute of Laboratory Medicine, Lund University, Lund, Sweden;* [d] *Department of Urology and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA;* [e] *Department of Experimental and Surgical Medicine, Urology Clinic, University "Tor Vergata", Roma, Italy;* [f] *Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands;* [g] *Department of Surgery, Oncology, and Gastroenterology—Urology Clinic, University of Padua, Padua, Italy;* [h] *Department of Urogynaecology, St Mary's Hospital, Imperial College, London, UK;* [i] *Department of Urology, Royal Hallamshire Hospital, Sheffield, South Yorkshire, UK*

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Abstract

Context: Several drugs are approved and available for the treatment of lower urinary tract symptoms (LUTS) in men and women. However, the vast majority of available data, upon which the approval and recommendation in guidelines are based, considered only the role of the monotherapies and did not evaluate possible combination therapies.
Objective: This systematic review analyzes the efficacy and adverse events of combination therapies for male and female LUTS.
Evidence acquisition: A systematic literature search in the PubMed/Medline, Web of Science, and Cochrane databases was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement to identify clinical trials, randomized controlled trials, meta-analyses, and guidelines on male and female LUTS combination therapy published from March 2012 to December 2017 for men (in order to update a previous men-focused work) and from January 1988 to December 2017 for women. A total of 58 papers were identified.
Evidence synthesis: The most studied combination therapy for the treatment of male LUTS is the α1-adrenoceptor antagonist/5α-reductase inhibitor combination. This combination seems to be more efficacious in terms of several outcome variables, in particular in men who have moderate-to-severe LUTS and are at risk of disease progression. Also in terms of nocturia improvements, this combination is significantly more effective than the monotherapy. The other often studied combination treatment, in both male and female patients with LUTS, was the combination of antimuscarinics (in particular solifenacin) and mirabegron. This combination seems to be more effective in comparison with the monotherapies with respect to urinary incontinence and urgency urinary incontinence episodes and several other objective and subjective parameters, without relevant increase of adverse events. The combination of hormone therapy and antimuscarinics in women with LUTS does not seem to be useful.
Conclusions: For the treatment of LUTS in men and women, combination therapy appears to be a promising option to optimize the efficacy of the available drugs for those who do not experience sufficient benefit with monotherapy. This add-on scenario offers the possibility to have a more tailored approach to the management of LUTS, always seeking the optimal balance between efficacy and tolerability for a given patient.
Patient summary: Some combination of drugs may offer advantages over monotherapies for the treatment of voiding and storage complaints in men and women.

* Corresponding author. Department Of Obstetrics and Gynecology, Urogynecology Unit, University of Insubria, Piazza Biroldi 1, 21100 Varese, Italy. Tel. +39-0332-299-309; Fax: +39-0332-299-307.
E-mail address: mauserati@hotmail.com (M. Serati).

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1. Introduction

Lower urinary tract symptoms (LUTS) distinguish storage, voiding, and postmicturition symptoms [1]. Many adults experience LUTS, and the prevalence of these symptoms increases with age [2]. The results of large population-based studies evaluating the prevalence of all LUTS using the definitions approved by the International Continence Society [1] are scarce; however, the prevalence of LUTS has been estimated [3]. Women report storage symptoms more frequently than men (59.2% vs 51.3%), whereas the opposite is true for voiding (men 25.7% vs women 19.5%) and postmicturition symptoms (men 16.9% vs women 14.2%). In men, the prevalence of all symptoms increases with advancing age, especially for those ≥60 yr of age. This trend is similar among women for urgency, nocturia, urge urinary incontinence (UUI), mixed urinary incontinence, other urinary incontinence (UI), intermittency, slow stream, and postmicturition dribble [3].

Depending on the severity threshold, the prevalence of male LUTS ranges from 10.3% to 25.1% [2,4,5]. While voiding LUTS are more frequent in men, the most common LUTS in women in reproductive age are any sort of UI, and for both groups childhood LUTS may be predictive of adult overactive bladder syndrome (OAB), consisting of urgency with or without incontinence, frequency, or nocturia [6,7]. The LUTS that define OAB were reported by 12.8% of women and 10.8% of men [3].

LUTS are common and they affect quality of life (QoL), including physical activity, sexual relations, social life, and future health [8–10]. Traditionally, LUTS in adult men were attributed to benign prostatic enlargement (BPE). However, the bladder has been recognized as a main contributor to male and female LUTS [11], and consequently, drugs targeting the bladder rather than the prostate could be considered part of the armamentarium of LUTS treatment. This view on the underlying working mechanism was followed by most guidelines [12–14].

Several drugs for the treatment of LUTS are available [12–14]: α1-adrenoceptor antagonists (α1-blockers), 5α-reductase inhibitors (5-ARIs), muscarinic receptor antagonists (antimuscarinics), β3-adrenoceptor agonists (β3-agonists), gabapentinoids, estrogens and progestins, and phosphodiesterase type 5 inhibitors (PDE5Is). Since LUTS may be multifactorial, the combined use of drugs with different modes of action and targeting different symptom complexes seems appealing. In response to previous reviews on this topic, this systematic review summarizes, in a methodical, evidence-based medicine approach, the evidence behind combination therapy for men and women with LUTS.

2. Evidence acquisition

A systematic literature search in the PubMed/Medline, Web of Science, and Cochrane databases was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [15] to identify clinical trials, randomized controlled trials (RCTs), meta-analyses, and guidelines on male and female LUTS combination therapy published from March 2012 to December 31, 2017 for men (in order to update a previous men-focused work from Füllhase et al. [16]) and from January 1988 to December 31, 2017 for women. The literature search was performed including the following MeSH search terms: lower urinary tract symptoms, voiding symptoms, storage symptoms, postmicturition symptoms, prostatic hyperplasia, overactive urinary bladder, urgency, frequency, nocturia, incontinence, adrenergic α1 receptor antagonists, 5α reductase inhibitors, muscarinic antagonists, vasopressins, phosphodiesterase 5 inhibitors, adrenergic beta 3 receptor agonists, phytotherapy, estrogens, progestins, and combination drug therapy.

Inclusion criteria in all search rounds were clinical trial, meta-analysis, RCT, guideline, male, female, and humans. Exclusion criteria were the following: (1) articles reporting on neurogenic LUTS, (2) articles reporting on LUTS in children, (3) articles reporting on monotherapy and not on a combination of two drugs or a combination of two phytotherapeutics, (4) nonsystematic review articles, and (5) guidelines that in their latest updated version were >3 yr old from the date of online publication.

Each extracted article was separately analyzed, classified, and labeled with a level of evidence according to a classification system modified from the Oxford Centre for Evidence-based Medicine [17]. Studies below the level of evidence 1b (RCTs) were excluded; the agreement on such exclusions was formulated via the Delphi approach [18]. However, we included secondary analyses from RCTs.

3. Evidence synthesis

3.1. Men: combination drug therapy for non-neurogenic LUTS

As previously mentioned, Füllhase et al. [16] systematically reviewed the combination drug therapy for non-neurogenic LUTS in men. The authors described the results of 49 papers published between January 1988 and March 2012. Our update search led to an additional 40 papers published between March 2012 and December 2017 (Fig. 1 and Supplementary Table 1).

3.1.1. Combination of α1-blockers with 5-ARIs

In 2013, Füllhase et al. [16] highlighted that the α1-blocker/5-ARI combination has been examined thoroughly and provides scientific evidence for the treatment of particular patient groups. This combination appeared to supersede monotherapy where long-term treatment is intended (>1 yr). Patients with an enlarged prostate (volume >30–40 ml) and who were at high risk for disease progression benefited most from this combination therapy. It remains unknown if the favorable effects of combination therapy could be maintained when treatment was continued for >6 yr [16].

Five studies have been published from March 2012 on α1-blocker/5-ARI combination therapy: three are post hoc analysis of previous trials and two are papers directly assessing the impact of medication on LUTS.

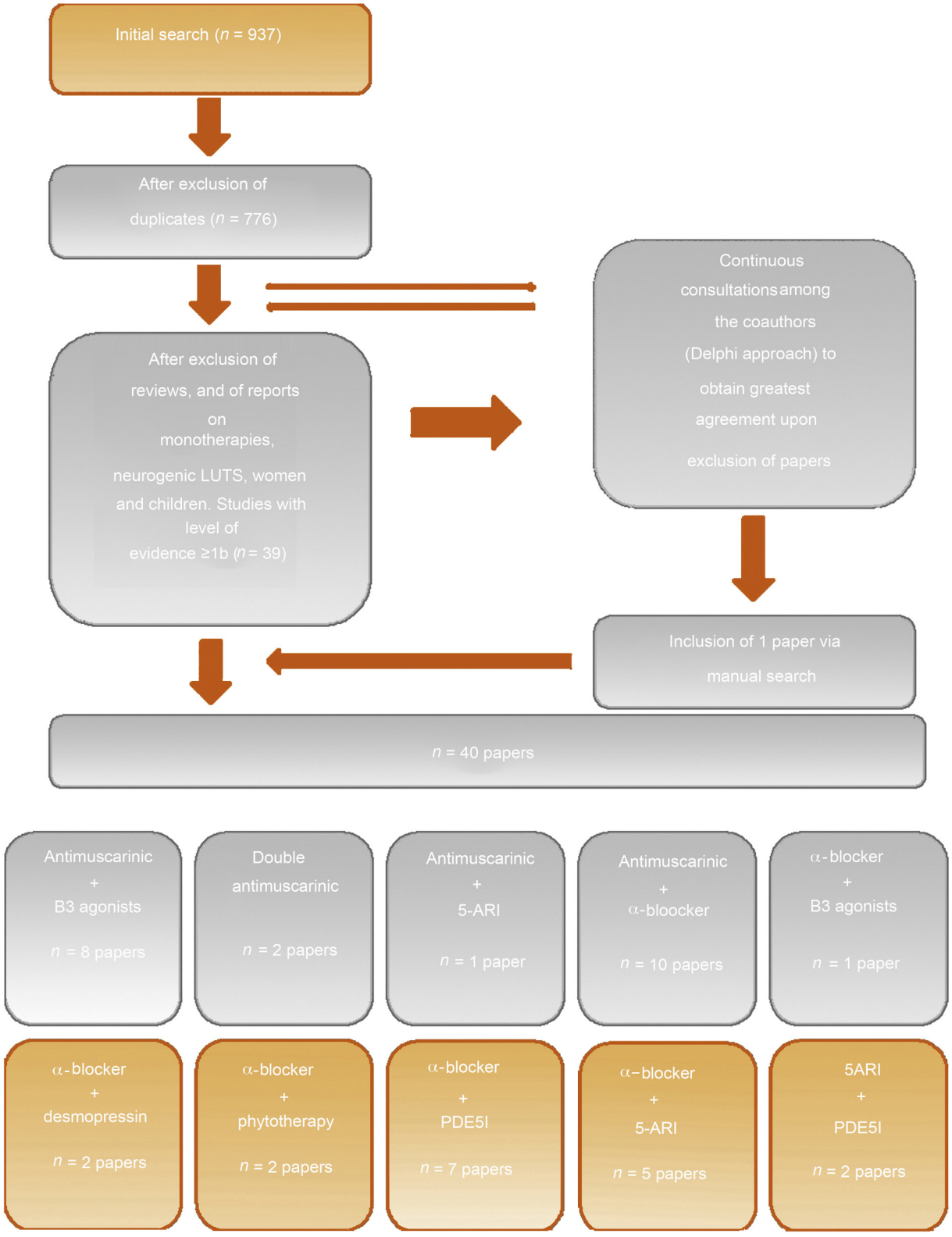

Fig. 1 – PRISMA "male" flow chart. 5-ARI = 5α-reductase inhibitor; LUTS = lower urinary tract symptoms; PDE5I =phosphodiesterase type 5 inhibitor; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

In 2013, Fwu et al examined the effects of doxazosin, finasteride, and combination therapy among men with benign prostatic hyperplasia (BPH) on QoL, which was the secondary outcome of the Medical Therapy of Prostatic Symptoms (MTOPS) study [19]. Medical Outcomes Study Short-Form 36 (MOS-SF-36), BPH Impact Index (BII), and International Prostate Symptom Score—QoL (IPSS-QoL) were used to assess the QoL during 4 yr. Men assigned to

doxazosin and combination experienced a statistically significant improvement in the BII at year 4 and a significant improvement in the IPSS-QoL compared with those assigned to placebo. The IPSS-QoL was significantly greater in men assigned to combination therapy and doxazosin, compared with those assigned to finasteride, over time. Considering longitudinal changes during 4 yr, a significant improvement in BII and IPSS-QoL scores was observed in men assigned to the drug groups compared with those assigned to placebo. However, there were no significant differences for the MOS-SF-36 subscales and summary scores when the drug groups were compared with the placebo group [20].

A post hoc 4-yr analysis was performed by Roehrborn et al. [21,22] to examine the influence of baseline variables on changes in IPSS, maximum urinary flow rate (Qmax), and IPSS-QoL in patients treated with either tamsulosin or dutasteride, alone or in combination, as part of the 4-yr Combination of Avodart and Tamsulosin (CombAT) study. Combination therapy resulted in a significantly greater improvement from baseline IPSS at 48 mo versus tamsulosin alone across all baseline subgroups. The benefit of combination therapy over dutasteride was confined to groups with lower baseline prostate volume (PV; <60 ml) and prostate-specific antigen (PSA; <4 ng/ml). In groups with baseline PV ≥60 ml and PSA ≥4 ng/ml, dutasteride and combination therapy show similar improvements in symptoms. Combination therapy resulted in significantly improved Qmax compared with tamsulosin but not dutasteride monotherapy. Qmax improvement appeared to increase with PV and PSA level in combination therapy individuals. The results showed that the combination therapy, dutasteride monotherapy, and tamsulosin monotherapy all improved Qmax but to different extents (combination therapy ≫ dutasteride ≫ tamsulosin), suggesting that dutasteride contributes most to the Qmax benefit in combination therapy [22].

In 2014, Lin et al. [23] investigated the treatment outcome of discontinuing one medication from 2-yr combination therapy for male with BPH/LUTS. Patients were randomly assigned to the 5-ARI discontinue (DC-5ARI) or the α-blocker discontinue (DC-α-blocker) group. All patients received combination therapy with dutasteride (0.5 mg/die) and doxazosin (4 mg/die) for 2 yr and then discontinued one drug for 12 mo. Resumption of combination therapy (primary outcome) was significantly more in the DC-5ARI than in the DC-α-blocker group (51.3% vs 31.0%; $p = 0.005$), the mean duration from discontinuing to resuming medication was 5.0 ± 4.4 mo in the DC-α-blocker and 7.8 ± 3.8 mo in the DC-5ARI group. Furthermore, PV progression (29.1% vs 8.0%; $p < 0.001$) and the need for transurethral resection of the prostate (TURP; 14.5% vs 7.1%; $p = 0.043$) were significantly higher in the DC-5ARI than in the DC-α-blocker group [23].

In 2014, Oelke et al. [24] assessed the impact of dutasteride plus tamsulosin combination therapy, compared with dutasteride or tamsulosin monotherapy, on nocturia (assessed using question 7 of the IPSS) using data from the 4-yr CombAT study [21]. Mean nocturia improvements were significantly superior with combination therapy than with either monotherapy. Reduction in nocturia score with combination therapy was significantly better than that with tamsulosin monotherapy across all baseline subgroups tested, except for men with previous 5-ARI use. Furthermore, among those with a baseline IPSS Q7 of ≥2, more patients with combination therapy had a score of <2 at month 48 (34%) compared with dutasteride (30%, $p = 0.018$) or tamsulosin (26%, $p < 0.0001$) [24].

In 2015, Roehrborn et al. [25] investigated whether a fixed-dose combination (FDC) of 0.5 mg dutasteride and 0.4 mg tamsulosin was more effective than watchful waiting with protocol-defined initiation of tamsulosin therapy if symptoms did not improve (WW-All) in treatment-naïve men with moderately symptomatic BPH at risk of progression. A total of 742 men were randomized to FDC or WW-All and followed for 24 mo. The change in IPSS at 24 mo (primary outcome) was significantly greater for FDC than for WW-All (−5.4 vs −3.6 points, $p < 0.001$), and FDC reduced the risk of BPH progression by 43.1% ($p < 0.001$) significantly improving the QoL (BII and IPSS-Q8). The safety profile of FDC was also consistent (Table 1) [25].

3.1.1.1. Comment. According to Füllhase et al. [16], all the studies confirmed the efficacy of combination therapy in particular patient groups with enlarged prostate and risk of BPH progression. Significant results in terms of QoL, IPSS, and nocturia have been assessed in the 4-yr MTOPS and CombAT post hoc analysis [20–22,24]. Combination therapy seems to reduce the risk of disease progression [23,25]. Furthermore, discontinuation of 5-ARIs in a combination regimen is significantly associated with progression of BPH and need for TURP [23]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy [12,21,22].

3.1.2. Combination of antimuscarinics/adrenergic β3 receptor agonists and 5-ARIs

Our literature search led to only one paper by Maeda et al. [26], who evaluated the clinical response and adverse events of solifenacin or mirabegron in BPH patients with persistent OAB symptoms after dutasteride treatment. Patients with residual OAB symptom score (OABSS) ≥5 and OABSS Q3 ≥2 after at least 6 mo treatment of dutasteride were administered 5 mg/d of solifenacin or 50 mg/d of mirabegron, and IPSS and OABSS were prospectively collected at 4 and 12 wk. Solifenacin 5 mg significantly reduced the IPSS, OABSS, and OABSS Q3 at 4 and 12 wk. Mirabegron treatment reduced IPSS and OABSS at 4 wk and reduced IPSS, OABSS, and OABSS Q3 at 12 wk. Four patients could not continue solifenacin owing to adverse events, although there was no significant difference in adverse event rates between the two groups [26].

3.1.2.1. Comment. Although the add-on therapy showed significant results in amelioration of the persistent OAB symptom after 5-ARI treatment, this study is probably underpowered for the outcome and has a relatively small sample size (Table 2).

Table 1 – Men: alpha-blocker and 5-ARI combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Fwu et al (2013) [20]	1b	2001–2005	2872/2872	Doxazosin 4–8 mg + finasteride 5 mg	209 wk	MOS-SF-36: PCS MCS	62.6 ± 7.3 yr	Age >50 yr AUA-SS 8–30 PSA 10 ng/ml Qmax 4–14 ml/s No limits on prostate size
4-yr CombAT Roehrborn et al (2014) [22]	1b	2009–2012	3195/3195	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d	209 wk	IPSS, Qmax, IPSS-QoL	60–71.5 yr, 35–68.1 ml	Patients ≥50 yr of age with a clinical diagnosis of BPH, IPSS ≥12 points, PV ≥30 ml by transrectal ultrasound (TRUS), total serum PSA level ≥1.5 ng/ml, and Qmax >5 and ≤15 ml/s with a minimum voided volume of ≥125 ml
Lin et al (2014) [23]	1b	NR	230/230	Discontinuation after 2 yr therapy with doxazosin 4 mg/d + dutasteride 0.5 mg/d	52 wk	BPH progression criteria as follows: total score of IPSS increase ≥4, Qmax decrease ≥2 ml/s, TPV increase ≥20%, PVR increase by 50% compared with baseline values, and the occurrence of acute urinary retention or the need for TURP	75.8 ± 8.52 yr	>45 yr with symptomatic BPH. IPSS >8, QoL-I >4, TPV >30 ml, Qmax <15 ml/s with minimal voided volume >125 ml
Oelke et al (2014) [24]	1b	2009–2012	4722/4722	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d	209 wk	IPSS Q7	66.1 ± 7.0 yr 55.0 ± 23.5 ml	Patients ≥50 yr of age with a clinical diagnosis of BPH, IPSS ≥12 points, PV ≥30 ml by TRUS, total serum PSA level ≥1.5 ng/ml, and Qmax >5 and ≤15 ml/s with a minimum voided volume of ≥125 ml
CONDUCT Roehrborn et al (2015) [25]	1b	2010–2013	592/592	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d	104 wk	IPSS	66.3 ± 7.78 yr 51.0 ± 18.17 ml	Men aged ≥50 yr, with a confirmed clinical diagnosis of BPH and moderate LUTS (IPSS of 8–19), prostate volume ≥30 cc by TRUS (at screening) and total serum PSA ≥1.5 ng/ml

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Fwu et al (2013) [20]	Doxazosin 4–8 mg MOS-SF-36: PCS:–2.34, MCS: 0.40	Finasteride 5 mg MOS-SF-36: PCS:–1.61, MCS:–0.59	NA	NA	NA	MOS-SF-36: PCS:–2.63, MCS:–0.54	Doxazosin 4–8 mg + finasteride 5 mg MOS-SF-36: PCS:–2.49, MCS:–0.33 Significant vs baseline	–	–	–	–	–

Table 1 (*Continued*)

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
4-yr CombAT Roehrborn et al (2014) [22]	Tamsulosin 0.4 mg/d	Dutasteride 0.5 mg/d	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d IPSS, Qmax, IPSS-QoL significant vs monotherapy	–	–	–	–	–
Lin et al (2014) [23]	Dutasteride discontinuation Overall BPH/LUTS progression: 83.8%	Doxazosin discontinuation Overall BPH/LUTS progression: 88.5%	NA	NA	NA	NA	–	–	–	–	–	–
Oelke et al (2014) [24]	Tamsulosin 0.4 mg/d IPSS Q7 48-mo score <2: 26%.	Dutasteride 0.5 mg/d IPSS Q7 48-mo score <2: 30%.	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d IPSS Q7 48-mo score <2: 34% Significant vs monotherapy	–	–	–	–	–
CONDUCT Roehrborn et al (2015) [25]	NA	NA	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + dutasteride 0.5 mg/d IPSS:–5.4 Significant vs WW-All	WW-All IPSS:–3.6	–	–	–	–

5-ARI = 5α-reductase inhibitor; AUA = American urological Association; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; MCS = mental summary score; MOS-SF-36 = Medical Outcomes Study Short-Form 36; NA = not available; NR = not reported; PCS = physical summary score; PSA = prostate-specific antigen; PV = prostate volume; PVR = postvoid residual; Qmax = maximum urinary flow rate; QoL = quality of life; SD = standard deviation; TPV = total prostate volume; TURP = transurethral resection of the prostate; WW-All = watchful waiting with protocol-defined initiation of tamsulosin therapy if symptoms did not improve.

Table 2 – Men: antimuscarinic and 5-ARI combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Maeda et al (2015) [26]	1b	2009–2011	50/50	Dutasteride + α-blocker + solifenacin 5 mg/d or mirabegron 50 mg/d	12 wk	Change from baseline to EOT of IPSS, OABSS, and quality of life score	71.6 ± 9.0 yr 48.6 ± 20.8 ml	Residual OAB symptom score (OABSS) ≥5 and OABSS Q3 ≥ 2 after at least 6 mo of treatment with DUT

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Maeda et al (2015) [26]	NA	NA	NA	NA	NA	NA	Dutasteride + α-blocker + solifenacin 5 mg/d IPSS:−3.1, OABSS:−2.7, OABSS Q3:−1.3 Significant before and after treatment	Dutasteride + α-blocker + mirabegron 50 mg/d IPSS:−3, OABSS:−0.8, OABSS Q3:−0.5 Significant before and after treatment	–	–	–	–

5-ARI = 5α-reductase inhibitor; DUT = dutasteride; EOT = end of treatment; IPSS = International Prostate Symptom Score; LoE = level of evidence; NA = not available; NR = not reported; OAB = overactive bladder; SD = standard deviation.

3.1.3. *Combination of antimuscarinics and adrenergic β3 receptor agonists*

The literature search led to a total of eight papers on the combination of solifenacin and mirabegron. The first of these papers is the MILAI Japanese add-on therapy study performed by Yamaguchi et al. [27]. This study enrolled 218 patients (35 male patients) with OAB who were being treated with solifenacin at a stable dose of 2.5 or 5 mg once daily for at least 4 wk. Patients meeting the eligibility criteria continued to receive solifenacin (2.5 or 5 mg once daily) and additional mirabegron (25 mg once daily) for 16 wk (increasable to 50 mg after 8 wk). Significant improvement was seen for changes in OAB-q SF symptom bother score (range from–16.31 to–22.25), mean OAB-q SF total health-related QoL (HRQoL) score (range from 12.56 to 17.34), micturitions/24 h (range from–1.89 to–2.36), urgency episodes/24 h (range from–1.57 to–2.59), urgency UI episodes/24 h (range–1.06 to–1.32), and mean voided volume (MVV)/micturition (range 29.865–36.957 ml) from baseline to end of treatment (EOT) in all groups. These results highlighted that the add-on therapy with mirabegron and solifenacin may provide an attractive therapeutic option. The most common drug-related adverse event was constipation (highest incidence in the solifenacin 5 mg + mirabegron 25 mg group); dry mouth was reported by only one patient (in the solifenacin 2.5 mg + mirabegron 50 mg group). No acute urinary retention (AUR) was noted, and no notable changes from baseline were seen for mean postvoid residual (PVR) volume in any treatment group [27]. This is an add-on study with a parallel design that generally requires a large number of patients for the analysis. Therefore, the main limitation is due to the not adequately powered outcomes. This concept was deepened by Abrams et al. [28] in the SYMPHONY trial with the aim to understand whether the mirabegron and solifenacin combination therapy might improve efficacy in the treatment of OAB symptoms while reducing solifenacin side effects. A total of 1306 patients (33.6% male patients) were randomized to 12 wk of treatment in one of 12 groups: six combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), five monotherapy groups (solifenacin 2.5, 5, or 10 mg, or mirabegron 25 or 50 mg), and the placebo group. Results showed that compared with solifenacin 5 mg monotherapy, all combinations with solifenacin 5 or 10 mg significantly improved the MVV (primary outcome) with adjusted differences ranging from 18.0 to 26.3 ml. Three combination groups significantly reduced micturition frequency compared with solifenacin 5 mg (ranging from–0.80 to–0.98). Five of six combinations significantly reduced urgency episodes compared with solifenacin 5 mg (ranging from–0.98 to–1.37). Constipation was slightly increased with combination therapy in the absence of major adverse events [28]. Benefits of different combinations of mirabegron and solifenacin (2.5/5/10 + 25/50 mg and their respective monotherapies compared with placebo and solifenacin 5 mg) on HRQoL based on patient-reported outcomes (PROs) were subsequently evaluated. Micturition frequency normalization and PROs (OAB-q and Patient Perception of Bladder Condition [PPBC]) were

significantly greater in combinations 10 + 25 and 5 + 50 mg versus solifenacin 5 mg alone [29].

Elderly men with severe symptoms of OAB were enrolled by Kosilov et al. [30]. Of the total 232 patients, 95 male patients were split into four groups: group A was treated with mirabegron 50 mg/d/6 wk, group B with solifenacin 10 mg/d/6 wk, group C with the same doses of both drugs simultaneously/6 wk, and group D with placebo. Monitoring was carried out using OABq, bladder diaries, and urodynamic examination. In group C, results significantly improved from baseline (UI: 5.1–1.6/d, $p \leq 0.01$; micturition/24 h: 9.1–5.3, $p \leq 0.01$; PVR 19.4–29.9, $p \leq 0.01$) versus monotherapy ($p \leq 0.05$). Furthermore, side effects did not differ significantly from monotherapy groups [30].

In 2016, Drake et al. [31] published the BESIDE trial evaluating the efficacy, safety, and tolerability of the combination of solifenacin 5 mg and mirabegron 50 mg versus solifenacin 5 or 10 mg in OAB patients remaining incontinent after 4 wk of solifenacin 5 mg. At EOT, combination was superior to solifenacin 5 and 10 mg with significant improvements in daily incontinence (primary endpoint–1.80 vs–1.53 vs–1.63, $p = 0.003$ and $p = 0.01$, respectively). Combination was superior to solifenacin 5 and 10 mg with regard to urgency episodes/24 h (–2.95 vs–2.41 vs–2.54, $p < 0.001$ and $p = 0.007$) and MVV/micturition (28 vs 16.5 vs 20.3 ml, $p < 0.001$ and $p = 0.005$). Absence of a significant improvement in nocturia with combination versus solifenacin 5 and 10 mg was reported. All treatments were well tolerated. The incidence of adverse events was lowest with solifenacin 5 mg (33.1%), highest with solifenacin 10 mg (39.4%), and 35.9% with combination; no AUR occurred [31]. Evaluation of PRO data from the BESIDE trial was then performed by Herdman et al. [32]. At the EOT, only the OAB-5D (derived from OAB-q) showed a statistically significant benefit for combination versus solifenacin alone. The same authors published three BESIDE post hoc analyses underlining that the combination therapy has no synergistic effect on cardiovascular safety [33]. The absence of clinically relevant changes in PVR volume has been observed in the BESIDE study even though it enrolled a relatively small male cohort (approximately 25% of the overall population) [34]. Finally, Gibson et al. [35] ensured that efficacy and safety of combination therapy is maintained in older patients (>65 yr).

In 2017, the SYNERGY study was performed by Herschorn et al. [36], evaluating solifenacin 5 mg combined with mirabegron (25 or 50 mg) compared with monotherapy. A total of 3398 patients were enrolled (33% male patients), and coprimary efficacy variables considered were change from baseline to EOT in the mean number of UI episodes/24 h and micturitions/24 h, assessed using a 7-d electronic micturition diary. Combination of solifenacin 5 mg + mirabegron 50 mg was superior to solifenacin 5 mg for UI (adjusted difference of–0.20 UI episodes/24 h) but not to mirabegron 50 mg alone. All active treatment groups had greater improvements in UI episodes/24 h vs placebo. For micturitions/24 h, adjusted change from baseline to EOT was greater in the combined therapy groups versus monotherapy groups and versus placebo group (S5 + M25:–0.85; S5 + M50:–0.95) higher than with mirabegron monotherapy (25 mg:–0.36; 50 mg:–0.39) and solifenacin 5 mg (–0.56). There was a slightly increased frequency of mild adverse events, with AUR and PVR increasing in the combined therapy groups versus monotherapy and placebo groups. This is the largest OAB study to date on combined therapy with solifenacin and mirabegron, which provided consistent improvements in efficacy compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally being consistent with an additive effect [36]. PROs were the subject of a separate manuscript, including change from baseline to EOT in OABq, HRQoL total score, PPBC, Treatment Satisfaction Visual Analogue Scale, and responder analyses. All the PROs showed that combination therapy provided clear improvements and an additive effect versus monotherapy [37].

3.1.3.1. Comment. Mirabegron has been studied in OAB patients with incontinence despite antimuscarinic therapy either as an add-on therapy or as a priori combination approach. All the RCTs presented had a predominantly female study population and did not report the results separately by gender. This could have led to an underpowered calculation of the outcomes for the male population. This could have influenced the statistical significance of the results leading to less clinically meaningful data. However, all the RCTs focused on the additive efficacy effect of combination therapy on OAB symptoms versus monotherapy and on the safe tolerability profile. Studies were rarely powered for safety outcomes (Table 3).

3.1.4. Combination of antimuscarinics (double antimuscarinic combination therapy)

Combination of solifenacin and trospium was described in two RCTs by Kosilov et al. [38]. The first study enrolled 79 men. All patients underwent a urodynamic examination before and 2 mo after treatment. Patients were randomized into the following groups: A1: trospium 30 mg/d + solifenacin 10 mg/d; A2: trospium 15 mg/d + solifenacin 5 mg/d; and A3: placebo. Groups of elderly patients with moderate symptoms of OAB who were treated with standard- and low-dose trospium and solifenacin demonstrated a significant increase in the median values of reflex volume, bladder capacity, and detrusor compliance, and a decrease in the frequency of urination and urinary urgencies. The frequency of episodes of incontinence (EI) in groups A1 and A2 decreased significantly in comparison with the initial data. The percentage of patients with a significant decrease (EI $\geq$ 1.0) among those treated with standard- and low-dose trospium and solifenacin increased synchronously, leading to the consideration that low-dose trospium and solifenacin provides significant clinical and urodynamic effects in elderly patients with moderate symptoms of OAB [38]. The combination of two antimuscarinics with the same mechanism of action could underline that outcomes are better when an appropriate dosing is considered for each of them. The limitation of this study is that the mix-gender approach may be adequately powered for effects in the overall group and not for effects within each gender,

Table 3 – Men: antimuscarinic and beta-3 agonist combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
SYNERGY Robinson et al (2017) [37]	1b	NR	783/3398	Solifenacin 5 mg + mirabegron (25 or 50 mg)	18 wk	Change from baseline to EOT in HRQoL (OABq) and PROs (PPBC) and TS-VAS	57.4 ± 13.4 yr PV NR	≥18 yr with wet OAB for ≥3 mo who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-d micturition diary
SYNERGY Herschorn et al (2017) [36]	1b	NR	783/3398	Solifenacin 5 mg + mirabegron (25 or 50 mg)	18 wk	Change from baseline to EOT in the mean number of UI episodes/24 h and micturitions/24 h	57.4 ± 13.4 yr PV NR	≥18 yr with wet OAB for ≥3 mo who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-d micturition diary
BESIDE Herdman et al (2017) [32]	1b	NR	353/2174	Solifenacin 5 mg + mirabegron 50 mg	20 wk	Change from baseline to EOT in the EQ-5D-5L and OAB-5D	57 ±13.2 yr PV NR	≥18 yr with OAB for ≥3 mo who recorded ≥2 UI episodes/24 h. After 4 wk of single-blind daily solifenacin 5 mg, patients remaining incontinent at baseline were randomized
BESIDE Drake et al (2016) [31]	1b	NR	353/2174	Solifenacin 5 mg + mirabegron 50 mg	20 wk	Change from baseline to EOT in the mean number of UI episodes/24 h	57 ± 13.2 yr PV NR	≥18 yr with OAB for ≥3 mo who recorded ≥2 UI episodes/24 h. After 4 wk of single-blind daily solifenacin 5 mg, patients remaining incontinent at baseline were randomized
Symphony Abrams et al (2017) [29]	1b	2013	439/1306	Solifenacin (2.5, 5, 10 mg) + mirabegron (25 and 50 mg)	12 wk	Change from baseline to EOT in HRQoL (OABq) and PROs (PPBC)	54.6 ± 13.4 yr PV NR	≥18 yr with symptoms of OAB for 3 mo. ≥8 micturitions per 24 h, ≥1 urgency episode/24 h (with or without incontinence), based on a 3-d electronic patient micturition diary
Symphony Abrams et al (2015) [28]	1b	2013	439/1306	Solifenacin (2.5, 5, 10 mg) + mirabegron (25 and 50 mg)	12 wk	Change from baseline to EOT in MVV	54.6 ± 13.4 yr PV NR	≥18 yr with symptoms of OAB for 3 mo. ≥8 micturitions per 24 h, ≥1 urgency episode/24 h (with or without incontinence), based on a 3-d electronic patient micturition diary
MILAI Yamaguchi et al (2015) [27]	1b	2014	35/218	Solifenacin (2.5 and 5 mg) + mirabegron (25 and 50 mg)	18 wk	Changes from baseline in OABSS total score, OAB-q-SF score, mean number of micturitions/24 h, mean number of urgency episodes/24 h, mean number of UI episodes/24 h, mean number of urgency UI episodes/24 h, MVV, and mean number of nocturia episodes/night	64.6 ± 9.97 yr PV NR	≥20 yr with OAB, previously treated with solifenacin at a stable dose of 2.5 or 5 mg once daily for at least 4 wk. OABSS total score of ≥3 points and a question 3 OABSS score of ≥2 points

Table 3 (*Continued*)

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Kosilov et al (2015) [30]	1b	NR	95/232	Solifenacin 10 mg + mirabegron 50 mg	6 wk	Change from baseline to EOT in MVV, postvoid residual, episodes of incontinence and micturitions	71,2 ± NR yr PV NR	≥65 yr, who suffer from severe symptoms of OAB (episodes of incontinence ≥3/d)

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
SYNERGY Robinson et al (2017) [37]	Solifenacin 5 mg HRQoL: +22.7 Significant vs placebo PPBC:−1.3 Significant vs placebo TS-VAS: 2.3 Significant vs placebo	Mirabegron 25 mg HRQoL: +21.6 Significant vs placebo PPBC:−1.2 Significant vs placebo TS-VAS: 2.2 Significant vs placebo	Mirabegron 50 mg HRQoL: +23.1 Significant vs placebo PPBC:−1.3 Significant vs placebo TS-VAS: 2.2 Significant vs placebo	NA	NA	HRQoL: +17 PPBC:−0.9 TS-VAS: 1.4	Solifenacin 5 mg/ mirabegron 25 mg HRQoL: +26.9 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 PPBC:−1.5 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 TS-VAS: 2.5 Significant vs placebo, vs mirabegron 25, not vs solif 5 mg	Solifenacin 5 mg/ mirabegron 50 mg HRQoL: +27.5 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 50PPBC:−1.7 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 TS-VAS: 2.6 Significant vs placebo, not vs mirabegron 25, not vs solif 5 mg	–	–	–	–
SYNERGY Herschorn et al (2017) [36]	Solifenacin 5 mg Zero UI/24 h: 177, not significant vs placebo Frequency normalization: 186, significant vs placebo	Mirabegron 25 mg Zero UI/24 h: 166, not significant vs placebo Frequency normalization: 172, significant vs placebo	Mirabegron 50 mg Zero UI/24 h: 188, significant vs placebo Frequency normalization: 163, significant vs placebo	NA	NA	Zero UI/24 h: 155 Frequency normalization: 128	Solifenacin 5 mg + mirabegron 25 mg Zero UI/24 h: 417, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg Frequency normalization: 422, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg	Solifenacin 5 mg + mirabegron 50 mg Zero UI/24 h: 426, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg Frequency normalization: 429, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg	–	–	–	–
BESIDE Herdman et al (2017) [32]	Solifenacin 5 mg EQ-5D-5L: 0.040 OAB-5D: 0.085	Solifenacin 10 mg EQ-5D-5L: 0.044 OAB-5D: 0.087	NA	NA	NA	NA	Solifenacin 5 mg + mirabegron 50 mg EQ-5D-5L: 0.059 OAB-5D: 0.107 Significant vs solifenacin 5 mg and vs solifenacin 10 mg	–	–	–	–	–
BESIDE Drake et al (2016) [31]	Solifenacin 5 mg UI/24 h:−1.54	Solifenacin 10 mg UI/24 h:−1.63	NA	NA	NA	NA	Solifenacin 5 mg + mirabegron 50 mg UI/24 h:−1.82, significant vs solifenacin 5 mg and vs solifenacin 10 mg	–	–	–	–	–

Table 3 (*Continued*)

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Symphony Abrams et al (2017) [29]	Solifenacin 2.5 mg HRQoL: +2.6 Not significant vs placebo PPBC: +3.1 Not significant vs placebo	Solifenacin 5 mg HRQoL:−0.3 Not significant vs placebo PPBC:−1.3 Not significant vs placebo	Solifenacin 10 mg HRQoL: +23.5 Not significant vs placebo and solif 5 mg PPBC:−1.5 Not significant vs placebo and solif 5 mg	Mirabegron 25 mg HRQoL: +20.2 Not significant vs placebo PPBC:−1.4 Not significant vs placebo	Mirabegron 50 mg HRQoL: +23.1 Not significant vs placebo PPBC:−1.5 Not significant vs placebo	HRQoL: +22 PPBC:−1.4	Solifenacin 2.5 mg/ mirabegron 25 mg HRQoL: +22.7 Not significant vs placebo, not significant vs solifenacin 5 mg alone PPBC:	Solifenacin 2.5 mg/ mirabegron 50 mg HRQoL: +22.7 Not significant vs placebo, not significant vs solifenacin 5 mg alone PPBC:−1.4 Not significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg HRQoL: +26 Not significant vs placebo, significant vs solifenacin 5 mg alone PPBC:−1.7 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg HRQoL: +28.4 Significant vs placebo and vs solifenacin 5 mg alone PPBC:−1.8 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 25 mg HRQoL +27.4 Significant vs placebo and vs solifenacin 5 mg alone PPBC:−1.8 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 50 mg HRQoL: +27 Not significant vs placebo, significant vs solifenacin 5 mg alone PPBC:−1.6 Not significant vs placebo, not significant vs solifenacin 5 mg alone
Symphony Abrams et al (2015) [28]	Solifenacin 2.5 mg + 36.4 ml Significant vs placebo	Solifenacin 5 mg +36 ml Significant vs placebo	Solifenacin 10 mg +36.2 ml Significant vs placebo but not significant vs solifenacin 5 mg alone	Mirabegron 25 mg +25 ml Not significant vs placebo	Mirabegron 50 mg +35 ml Significant vs placebo	+14 ml	Solifenacin 2.5 mg/ mirabegron 25 mg +39.4 ml Significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 2.5 mg/ mirabegron 50 mg +42 ml Significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg +54 ml Significant vs placebo, vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg +54.2 ml Significant vs placebo, vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 25 mg +58 ml Significant vs placebo, vs solifenacin 5 mg alone	Solifenacin10 mg/ mirabegron 50 mg +62.3 ml Significant vs placebo, vs solifenacin 5 mg alone
MILAI Yamaguchi et al (2015) [27]	NA	NA	NA	NA	NA	NA	Solifenacin 2.5 mg/ mirabegron 25 mg + 29.8 ml Significant vs solifenacin 5 mg alone	Solifenacin 2.5 mg/ mirabegron 50 mg +33.0 ml Significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg +34.1 ml Significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg +36.9 ml Significant vs solifenacin 5 mg alone	–	–
Kosilov et al (2015) [30]	Mirabegron 50 mg/d MVV: +35 ml, PVR: +11.5 ml, EI:−2.3/day, micturitions:−3.7/d Significant before and after treatment	Solifenacin 10 mg/d MVV: +64 ml, PVR: +9 ml, EI:−2.2/d, micturitions:−3.4/d Significant before and after treatment	NA	NA	NA	MVV: +12 ml, PVR:−3 ml Not significant before and after treatment	Solifenacin 10 mg + mirabegron 50 mg MVV: +94 ml, PVR: +10.5 ml, EI:−3.8/d, micturitions:−4/d Significant vs mirabegron alone and vs solifenacin alone	–	–	–	–	–

EI = episodes of incontinence; EOT = end of treatment; HRQoL = health-related QoL; LoE = level of evidence; MVV = mean voided volume; NR = not reported; OAB = overactive bladder; OABSS = OAB symptom score; PV = prostate volume; PPBC = Patient Perception of Bladder Condition; PRO = patient-reported outcome; PVR = postvoid residual; QoL = quality of life; SD = standard deviation; solif = solifenacin; TS-VAS = Treatment Satisfaction Visual Analogue Scale; UI = urinary incontinence.

probably limiting the clinical relevance. The second study assessed the effectiveness of combined standard-dosed solifenacin and trospium for the management of symptoms of OAB in male patients after initial treatment with tamsulosin. A total of 417 men with diagnosed prostatic obstruction received 2-mo treatment with tamsulosin 0.4 mg/d; 139 patients (45.8% from the initial group) revealed OAB symptoms and were prescribed solifenacin 5 mg + trospium 5 mg for 2 mo. Patients taking placebo remained the same. Night-time frequency, urgency, UUI, and Qmax were significantly improved by the combination therapy [39].

3.1.4.1. Comment. Despite a small sample size, the first RCT assessed the clinical and urodynamic efficacy of low-dose trospium and solifenacin in elderly patients with moderate symptoms of OAB, probably creating a synergetic effect that makes it possible to decrease the dose of each drug [38]. The attempt to study the influence of the combination of standard-dosed trospium and solifenacin as an add-on therapy to tamsulosin on residual symptoms of OAB led to interesting clinical results [39]. However, the use of three different medications could represent a limitation in terms of costs and adherence, especially for elderly patients in polytherapy regimens (Table 4).

3.1.5. Combination of antimuscarinics and α1-blockers

Literature search led to 10 clinical studies on α1-blocker/antimuscarinic combinations. Four are add-on studies, in which antimuscarinics have been added to baseline α1-blocker therapy. Five trials prospectively compared the antimuscarinic with placebo, α1-blockers, and α1-blocker/antimuscarinic combination, and one trial compared the efficacy of initial α1-blocker/antimuscarinic combined therapy with the same drug add-on combination therapy.

In 2012, Kaplan et al. [40] evaluated flexible-dose fesoterodine versus placebo in men with persistent OAB symptoms despite receiving α-blocker treatment. A total of 943 men after receiving an α-blocker for ≥6 wk were randomized and received at least one dose of study treatment (fesoterodine, $n = 471$; placebo, $n = 472$). Drug dose was adjusted by week 8. Although improvements in micturitions (–1.7, $p = 0.009$) and OAB-q symptom bother score (–15.2 ± 0.9, $p = 0.007$) were significantly greater with fesoterodine at week 12, and improvements in micturitions (–0.8, $p = 0.006$), severe urgency episodes (–1.7, $p = 0.006$), IPSS storage score (–1.8 ± 0.1, $p = 0.022$), OAB-q symptom bother score (–11.6 ± 0.8, $p = 0.004$), and OAB-q HRQoL (8.7 ± 0.8, $p = 0.041$) were significant at week 4, changes from baseline to week 12 in urgency episodes (primary endpoint) in the fesoterodine (–3.2) and placebo (–2.9) groups were not significantly different ($p = 0.196$). Dry mouth (fesoterodine 21%; placebo 6%) and constipation (fesoterodine 6%; placebo 2%) were the most common adverse events [40]. Konstantinidis et al. [41] performed another add-on study on patients who were treated initially with tamsulosin 0.4 mg for 1 wk. Patients still experiencing inconvenient LUTS were randomized into two groups. The first group received a combination therapy of tamsulosin and fesoterodine, while the second continued the therapy with the single administration of tamsulosin for an additional 4-wk period. A statistically significant improvement appeared in the combination group regarding the storage and the total IPSS values between the visits (16.1 ± 1.8 to 13.7 ± 1.5). The study presents a very small sample size, may be underpowered, and has a short follow-up [41]. Similar results were obtained in the other add-on studies. The effects of add-on treatment with imidafenacin on OAB symptoms despite tamsulosin treatment in BPH patients were evaluated by Takeda et al. [42] in the ADDITION study. Patients ($n = 308$) with urinary urgency at least once per week and total OABSS of ≥3 points after ≥8-wk treatment with tamsulosin were randomized to receive tamsulosin 0.2 mg/d alone or tamsulosin 0.2 mg/d + imidafenacin 0.1 mg twice per day. The change from baseline to 12 wk in total OABSS (–4.2 vs–2.1), improvements in frequencies of daytime urination (–1.4 vs–0.3), night-time urination (–0.4 vs–0.1), urinary urgency (–1.7 vs–0.7), UUI (–1.1 vs–0.5), IPSS (–5.4 vs–3.4), IPSS-QoL (–1.6 vs–0.8), and BII (–3 vs–1.3) were significantly higher from 4 wk through 12 wk in the imidafenacin group. Between-group difference in PVR volume at 12 wk was not significant (–1.74 ml, 95% confidence interval–8.19 to 4.72), and no events of urinary retention were reported [42]. In 2015, Yokoyama et al. [43] evaluated the efficacy and safety of imidafenacin as add-on therapy for male LUTS with nocturia and nocturnal polyuria despite receiving a stable dose of an α1-blocker. Patients were randomized to control (α1-blocker), imidafenacin twice per day (α1-blocker + 0.1 mg imidafenacin twice daily), or imidafenacin nightly (α1-blocker plus 0.1 mg imidafenacin nightly) group; the treatment period was 8 wk. Compared with the controls, imidafenacin twice per day and imidafenacin nightly patients had a significantly lower night-time frequency (changes from baseline: 0.1 ± 0.8 in control,–0.6 ± 0.9 in imidafenacin twice per day, and–0.4 ± 1.0 in imidafenacin nightly). The hours of undisturbed sleep (40.9 ± 12 vs 14.9 ± 11 min) and N-QoL score (8.99 ± 2.13 vs 11.22 ± 2) were significantly improved in the imidafenacin twice per day group, although not in the imidafenacin nightly group. Nocturnal urine volume was significantly reduced in the nightly group, although the total urine volume remained unchanged. There were no reports of urinary retention. This RCT was open label and not double blinded [43].

Among the prospective combination studies, Kaplan et al. [44] focused on the safety of a once-daily combination of solifenacin (6 or 9 mg) and tamsulosin oral 0.4 mg compared with placebo in men with LUTS and bladder outlet obstruction (BOO). Although PV and PSA level were not measured, the authors found that both active treatment groups were noninferior to placebo at EOT for PdetQmax and Qmax, and that the mean change from baseline PVR was significantly higher at all time points for tamsulosin 0.4 mg + solifenacin 6 mg, and at weeks 2, 12, and EOT for tamsulosin 0.4 mg plus solifenacin 9 mg versus placebo. AUR was registered in one patient receiving tamsulosin 0.4 mg + solifenacin 6 mg [44]. In 2013, Sener et al. [45] evaluated long-term efficacy and safety of the use of

Table 4 – Men: double antimuscarinic combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Kosilov et al (2014) [38]	1b	2012	79/177	Trospium 15 mg/d + solifenacin 5 mg/d	16 wk	Change from baseline to EOT in MVV, postvoid residual, episodes of incontinence and micturitions	69.4 ± NR yr PV NR	Moderate symptoms of OAB who during the previous 5 yr (but not less than half a year before the study) had undergone monotherapy with antimuscarinic drugs with unsatisfactory or short-term and rapidly disappearing effect
Kosilov et al (2014) [38]	1b	2012	237	Trospium 5 mg/d + solifenacin 5 mg/d	8 wk	IPSS, OAB Awareness Tool (OAB-AT)	57.9 ± 8.3 yr 27.8 ± 7.3 ml	Prostatic obstruction (score 8–19 according to IPSS) and residual volume <100 ml, who had not taken tamsulosin before

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kosilov et al (2014) [38]	NA	NA	NA	NA	NA	Not significant before and after treatment	Trospium 15 mg/d + solifenacin 5 mg/d MVV: +106 ml, PVR: +11 ml, EI:−1.18/d, micturitions:−1.85/d Significant before and after treatment and vs standard dose antimuscarinics	Trospium 30 mg/d + solifenacin 10 mg/d MVV: +94 ml, PVR: +11 ml, EI:−1.08/d, micturitions:−3.59/d Significant before and after treatment	–	–	–	–
Kosilov et al (2014) [38]	NA	NA	NA	NA	NA	Not significant before and after treatment	Trospium 5 mg/d + solifenacin 5 mg/d IPSS and OAB-AT reduction significant vs placebo	–	–	–	–	–

EI = episodes of incontinence; EOT = end of treatment; IPSS = International Prostate Symptom Score; LoE = level of evidence; MVV = mean voided volume; NR = not reported; OAB = overactive bladder; PVR = postvoid residual; SD = standard deviation.

propiverine and terazosine combination. Patients were randomized into two groups: terazosine + placebo and terazosine + propiverine HCl. After 1-yr treatment, there was a significant improvement in IPSS (−12.8), OAB symptom (−15.3), Q8-QoL (−2.9), and Qmax (+1.8) values in the combination group. No patient left the study because of side effects. No patient suffered AUR after 1 yr of treatment [45]. These results were aligned with those coming from the NEPTUNE trial, which assessed the efficacy of an FDC of solifenacin and tamsulosin compared with placebo and compared with tamsulosin monotherapy [46]. A total of 1334 patients were randomized to placebo, tamsulosin 0.4 mg, solifenacin 6 mg + tamsulosin 0.4 mg, or solifenacin 9 mg + solifenacin 0.4 mg. Reductions in total IPSS and Total Urgency and Frequency Score (TUFS) were observed with both solifenacin 6 mg + tamsulosin (−7.0 and−8.1, respectively) and solifenacin 9 mg + tamsulosin (−6.5 and−7.6, respectively) compared with tamsulosin (−6.2 and−6.7, respectively) and placebo (−5.4 and−4.4, respectively). Solifenacin 6 mg + tamsulosin met all the prespecified success criteria for both primary endpoints, while solifenacin 9 mg + tamsulosin met success criteria compared with placebo but not compared with tamsulosin. AUR occurred in eight patients. Small increases in PVR volume were observed with both 6 and 9 mg FDC (3.8 and 12.3 ml), but were not clinically relevant [46]. The NEPTUNE II trial evaluated long-term efficacy (up to 52 wk) using solifenacin and tamsulosin. Reductions in total IPSS and TUFS during NEPTUNE were maintained for up to 52 wk of FDC treatment. Clinically relevant improvements were also observed for secondary efficacy endpoints (IPSS storage and voiding subscores, micturition diary variables, and QoL parameters) [47].

In 2014, Ko et al. [48] focused on how much the improvement of LUTS affected erectile function and which storage symptoms or voiding symptoms might have had the greatest effect on sexual function. A total of 187 patients were randomly assigned to receive either (1) tamsulosin 0.2 mg or (2) tamsulosin 0.2 mg and solifenacin 5 mg. At 4 and 12 wk, both groups showed statistically significant improvements in IPSS, OABSS, and QoL. The International Index of Erectile Function (IIEF)-5 score was not improved in either group at 12 wk (group 1, 13.66 ± 4.97 to 11.93 ± 6.14, $p = 0.072$ vs group 2, 13.19 ± 5.91 to 12.45 ± 6.38, $p = 0.299$), and the difference between the two groups was not significant ($p = 0.696$). Therefore, despite improvements in voiding symptoms and QoL, either tamsulosin monotherapy or combination therapy with solifenacin did not improve erectile function [48].

An interesting comparison of the clinical efficacy of initial combined therapy of tamsulosin and solifenacin with their add-on combination was performed by Lee et al. [49]. A total of 156 patients were randomized into the following two groups: group 1—treated with tamsulosin 0.2 mg/d for 4 wk and after 8 wk treated with the combination of tamsulosin 0.2 mg and solifenacin 5.0 mg daily; group 2—treated initially with tamsulosin 0.2 mg and solifenacin 5.0 mg combination for 12 wk. By the 4th week, there was no difference between the two groups regarding IPSS total score and voiding symptom score, although the IPSS storage symptom score was significantly lower in group 2 (−2.0 ± 0.2 vs−3.0 ± 0.2). Although at the 12th week, there was an improvement in IPSS storage symptom score, OABSS, and urgency symptoms compared with baseline in each group ($p < 0.001$), no statistical differences in storage indices were observed between the two groups at 12 wk. Hence, the results showed that earlier treatment with α1-blockers and anticholinergic agents may help improve storage symptoms and QoL earlier for patients with LUTS/BPH and OAB symptoms. AUR was reported for one patient in group 1 after the addition of solifenacin [49].

3.1.5.1. Comment. Although some RCTs present a small sample size and a short follow-up period, efficacy in patients with LUTS and OAB has been reported transversally either in add-on studies or in a priori combination ones. The use of flexible doses of a drug represents a limitation due to the possible exacerbation of the placebo response [40]. Promising results came from two open-label, not double-blind trials even in the absence of a placebo control [42,43]. Urodynamic studies assessed, on the one hand, the noninferiority of combination of tamsulosin and solifenacin to placebo at EOT in men with LUTS and BOO, and on the other hand, there was no statistical evidence of an increased risk of AUR, suggesting no negative effect on bladder function during voiding in these obstructed patients [45]. Combination of antimuscarinics and α1-blockers did not improve erectile dysfunction despite an improvement in storage symptoms [48]. Not all antimuscarinics have been tested, and long-term studies on the efficacy in men of any age with LUTS are not yet available. According to the European Association of Urology (EAU) guidelines, although AUR is a rare event in men, regular re-evaluation of IPSS and PVR urine is advised (Table 5) [12].

3.1.6. Combination of α1-blockers and adrenergic β3 receptor agonists

The search led to only one relevant RCT about the combination therapy with tamsulosin and mirabegron. Ichihara et al. [50] evaluated the efficacy and safety of add-on treatment with mirabegron for OAB symptoms remaining after tamsulosin treatment in men with benign prostatic obstruction (BPO). A total of 76 patients with BPO and OAB in treatment with tamsulosin were randomly allocated to receive 0.2 mg tamsulosin daily or 0.2 mg tamsulosin + 50 mg mirabegron daily for 8 wk. The add-on therapy was found to be effective and safe. OABSS during the treatment period was significantly improved in the combination versus monotherapy (−2.21 vs−0.87, $p = 0.012$) group. Furthermore, changes in scores for urinary urgency, daytime frequency, IPSS storage symptom subscore, and QoL index at 8 wk were significantly greater in the combination group. The mean change in PVR from baseline at 8 wk was 37.3 ml in the mirabegron add-on group, which was significantly greater than that in the monotherapy group ($p = 0.020$). AUR was observed in only one patient [50].

Table 5 – Men: antimuscarinic and alpha-blocker combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Kaplan et al (2012) [40]	1b	2007–2009	943/943	Fesoterodine 4 mg + α-blocker	12 wk	Mean change in the number of urgency episodes/24 h from baseline to week 12, IPSS, OABq	65.5 ± 9.1 yr 40.7 ± 22.2 ml	Men aged ≥ 40 yr who had received α -blocker treatment for at least 6 wk, mean ≥8 micturitions and ≥3 urgency episodes per 24 h in a 3-d bladder diary, and Patient Perception of Bladder Condition (PPBC; ie, score ≥3)
Kaplan et al (2013) [44]	1b	NR	192/192	Solifenacin 6 or 9 mg + tamsulosin OCAS	12 wk	Qmax and PdetQmax, IPSS	64.3 ± 7.6 yr	Men aged >45 yr with LUTS and BOO for 3 mo, total IPSS 8, BOO index 20, Qmax 12 ml/s, and voided volume 120 ml
Konstantinidis et al (2013) [41]	1b	2009–2011	47/47	Fesoterodine 4 mg + tamsulosin 0.4 mg daily	4 wk	IPSS	64.5 ± 4.5 yr 42.3 ± 8.4 ml	Men aged >50 yr, with LUTS, prostate volume <60 ml, and IPSS >13
Sener et al (2013) [45]	1b	2009–2012	100/100	Terazosin 2 mg/d + propiverine HCl 15 mg/d	52 wk	IPSS, IPSS4, QoL, OAB symptoms, PVR, and Qmax	54.7 ± 6.0 yr	>40 yr, IPSS >12, PSA <2.5, having OAB symptoms (>8 cycles of urination/24 h, >3 with urgency [or urge incontinence]/ 24 h), documented detrusor pressure >10 cmH_2O in urodynamic studies
Takeda et al (2013) [42]	1b	2010–2011	246/246	Tamsulosin 0.2 mg/d + imidafenacin 0.1 mg 2 times a day	12 wk	OABSS, IPSS	72.2 ± 7.4 yr 15.0 ± 16.0 ml	≥50 yr old, OABSS question 3 score ≥2 and a total OABSS of ≥3 points after treatment with tamsulosin for ≥8 wk, PVR urine <50 ml, and prostate volume 20 ml
NEPTUNE van Kerrebroeck et al (2013) [46]	1b	2010–2011	1334/1334	Solifenacin 6 or 9 mg + tamsulosin OCAS	12 wk	IPSS, TUFS	65.4 ± 8.1 yr 8.1 ± 14.0 ml	IPSS ≥13, maximum urinary flow rate (Qmax) 4.0–12.0 ml/s, two or more urgency episodes per 24 h of Patient Perception of Intensity of Urgency Scale grade 3 or 4, and eight or more micturitions per 24 h
NEPTUNE II Drake et al (2015) [47]	1b	2010–2012	1066/1066	Solifenacin 6 or 9 mg + tamsulosin OCAS	52 wk	IPSS, TUFS from baseline (NEPTUNE) to EOT (NEPTUNE II)	65.1 ± 8.11 yr 37.8 ± 13.9 ml	Patients with both storage and voiding LUTS, maximum urinary flow rate of 4.0–12.0 ml/s, prostate size <75 ml, and postvoid residuals 150 ml; those who completed the 12-wk, double-blind NEPTUNE study could continue in the 40-wk, open-label NEPTUNE II study

Table 5 (*Continued*)

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Ko et al (2014) [48]	1b	2011–2012	187/187	Tamsulosin 0.2 mg + solifenacin 5 mg/d	12 wk	IIEF5, IPSS, OABSS	61.09 ± 9.18 yr 28.71 ± 11.13 ml	Men 40 yr of age or older who had LUTS as indicated by an IPSS of >12, urinary frequency (≥8/d), urgency (≥1/d), and symptoms on a 3-d voiding diary were invited to participate. All sexually active ≥once per month regardless of IIEF score
Lee et al (2014) [49]	1b	2008–2009	156/156	Tamsulosin 0.2 mg + solifenacin 5 mg/d	12 wk	Early onsets of efficacy (4 wk) IPSS, QoL	61.2 ± 1.0 yr 32.4 ± 2.9 ml	Male, ≥50 yr, total IPSS ≥14 (voiding subscore ≥8 and storage subscore ≥6), IPSS QOL score ≥3, micturition frequency (≥8/24 h), urgency (≥1 micturition with urgency rating 3 per 24 h), prostate volume ≥20 cc by TRUS
Yokoyama et al (2015)	1b	2009–2011	152/152	α1-Blocker + imidafenacin 0.1 mg/2× a day or once nightly	8 wk	Night-time frequency and N-QoL	73.3 ± 6.7 yr 18.9 ± 16.8 ml	Men with persistent nocturia (≥2 voids/night) and LUTS including OAB symptoms (mean urinary frequency ≥8 times/24 h and ≥1 micturition-related urgency episode/wk), who had been receiving a stable dose of an α1-blocker for ≥1 mo

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kaplan et al (2012) [40]	NA	NA	NA	NA	NA	Placebo + α-blocker UI episodes:−2.9, IPSS:−4.4, OABq:−12.4	Fesoterodine 4 mg + α-blocker UI episodes:−3.2 (NS), IPSS:−4.4 (NS) OABq:−15.2, significant vs placebo	–	–	–	–	–
Kaplan et al (2013) [44]	NA	NA	NA	NA	NA	Qmax: +0.1, PdetQmax:−1.7, IPSS:−6.6	Solifenacin 6 mg + tamsulosin OCAS Qmax: +1.9, PdetQmax:−7.8, IPSS:−8 Not inferior to placebo	Solifenacin 9 mg + tamsulosin OCAS Qmax: +2.4, PdetQmax:−6.7, IPSS:−6.9 Not inferior to placebo	–	–	–	–
Konstantinidis et al (2013) [41]	Tamsulosin 0.4 mg/d IPSS:−0.7	NA	NA	NA	NA	NA	Fesoterodine 4 mg + tamsulosin 0.4 mg daily IPSS:−2.4 Significant vs tamsulosin alone	–	–	–	–	–

Table 5 (*Continued*)

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Sener et al (2013) [45]	Terazosin 2 mg/d + placebo IPSS:−5, IPSS4:−1.5, QoL: 0.2, OABSS:−2.3, PVR:−20 ml, Qmax: 1.5	NA	NA	NA	NA	NA	Terazosin 2 mg/d + propiverine HCL 15 mg/d IPSS:−12.8, IPSS4:−7.4, QoL: 2.9, OABSS:−15.3, PVR:−18 ml, Qmax: 1.8 Significant vs terazosin + placebo (except PVR, Qmax)	–	–	–	–	–
Takeda et al (2013) [42]	Tamsulosin 0.2 mg/d OABSS:−2.1, IPSS:−3.4	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg/d + imidafenacin 0.1 mg 2 times a day OABSS:−4.2, IPSS:−5.4 Significant vs tamsulosin alone	–	–	–	–	–
NEPTUNE van Kerrebroeck et al (2013) [46]	Tamsulosin OCAS 0.4 mg/die IPSS:−6.2, TUFS:−6.7 Significant vs placebo	NA	NA	NA	NA	IPSS:−5.4, TUFS:−4.4	Solifenacin 6 mg + tamsulosin OCAS IPSS:−7, TUFS:−8.1 Significant vs placebo and vs tamsulosin alone	Solifenacin 9 mg + tamsulosin OCAS IPSS:−6.5, TUFS:−7.6 Significant vs placebo and vs tamsulosin alone	–	–	–	–
NEPTUNE II Drake et al (2015) [47]	NA	NA	NA	NA	NA	NA	Solifenacin 6 or 9 mg + tamsulosin OCAS IPSS:−9.0, TUFS:−10.1 Significant before and after treatment	–	–	–	–	–
Ko et al (2014) [48]	Tamsulosin 0.2 mg IIEF5: 13.08, IPSS: 19.07, OABSS: 6.32	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg and solifenacin 5 mg/d IIEF5: 13.19, IPSS: 19.62, OABSS: 7.13 (significant vs tamsulosin alone)	–	–	–	–	–
Lee et al (2014) [49]	Tamsulosin 0.2 mg/die IPSS:−4.9, QoL:−0.6	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg/d + solifenacin 5 mg IPSS:−5.4, QoL:−1.1 Significant vs tamsulosin alone	–	–	–	–	–

Table 5 (*Continued*)

Trial	Change of effect score from baseline										
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Yokoyama et al (2015)	α1-Blocker Night-time frequency: 0.08, N-QOL: 4.51	NA	NA	NA	NA	NA	α1-Blocker + imidafenacin 0.1 mg/2× a day Night-time frequency:–0.57, N-QOL: +11.22 Significant vs baseline and vs control	α1-Blocker + imidafenacin 0.1 mg/once nightly Night-time frequency:–0.41, N-QOL: 8.99 Significant vs baseline and vs control	–	–	–	–

BOO = bladder outlet obstruction; EOT = end of treatment; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; NS = not significant; OAB = overactive bladder; OABSS = OAB symptom score; OCAS = oral controlled absorption system; PSA = prostate-specific antigen; PVR = postvoid residual; Qmax = maximum urinary flow rate; QoL = quality of life; SD = standard deviation; TRUS = transrectal ultrasound; TUFS = Total Urgency and Frequency Score; UI = urinary incontinence.

3.1.6.1. Comment. Although this study has a relatively short treatment duration and a small sample size, it underlined the efficacy of adding mirabegron in a special niche of patients with persisting storage symptoms not responding to α-blockers. In this Japanese study, the standard tamsulosin dose is 0.2 mg, which could provide some heterogeneity with other international results. Evidence on a fully effective dose still requires further studies (Table 6).

3.1.7. Combination of α1-blocker and desmopressin

Two studies on desmopressin add-on to tamsulosin therapy for nocturia were published. In 2013, Bae et al. [51] enrolled 216 patients, of whom 158 (76%) had nocturnal polyuria, 15 (7.2%) had decreased nocturnal bladder capacity, and 35 (16.8%) had nocturia due to both causes despite α-blocker treatment for a minimum of 4 wk. The optimum dose of oral desmopressin was determined during a 4-wk dose titration period, and this dose was maintained for 24 wk. The number of nocturnal voids significantly decreased from a baseline at the 24-wk visit (from 7 to 5.7, $p < 0.01$). The average IPSS total and subscores significantly decreased by 4 wk and were maintained at 24 wk. IPSS voiding subscores were significantly improved at 24 wk in patients younger than 65 yr compared with those in patients aged 65 yr or older. Hence, desmopressin add-on therapy for refractory nocturia has been considered effective and well tolerated [51]. These results were confirmed by Ahmed et al. [52], who included 248 patients with BPH and nocturia ≥2/night. Patients were randomized; group 1 received 3-mo treatment scheme of tamsulosin 0.4 mg/d and desmopressin 60 μg (D/T group), while group 2 received tamsulosin 0.4 mg only (T group). Frequencies of night voids decreased by 64.3% in the D/T group compared with 44.6% in the T group. The first sleep period significantly increased from 82.1 to 160.0 min and from 83.2 to 123.8 min in the D/T and T groups, respectively; significant differences between both groups were observed at the end of study ($p < 0.001$). IPSS, QoL, PVR volume, and Qmax were significantly improved compared with baseline without statistical difference between both groups. No serious adverse effects were reported in both groups (Table 7) [52].

3.1.7.1. Comment. Nocturia is one of the most bothersome LUTS. In a group of BPH patients with nocturia, despite the assumption of tamsulosin, the add-on therapy with desmopressin significantly improved nocturia. Hyponatremia is recognized as the most concerning adverse event of desmopressin therapy [51,52]. Although most patients are not symptomatic, assessment of serum sodium after starting therapy is recommended. Studies were rarely powered for safety outcomes.

3.1.8. Combination of α1-blockers and PDE5Is

Through the literature search, we found seven relevant studies on combination therapy of α1-blockers and PDE5Is (two studies on sildenafil, four on tadalafil, and one on vardenafil).

Öztürk et al. [53] compared the efficacy of alfuzosin 10 mg alone or in combination with sildenafil 50 mg in the

Table 6 – Men: alpha-blockers and beta-3 agonist combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Ichihara et al (2015) [50]	1b	2012–2013	76/76	Tamsulosin 0.2 mg/d + mirabegron 50 mg/d	8 wk	Change in the total OABSS, total IPSS, QoL, Qmax, PVR	74.5 ± 8.2 yr 34.2 ± 16.2 ml	≥50 with LUTS most likely secondary to BPO. Persistent OAB symptoms after 0.2 mg/d α-blocker tamsulosin monotherapy for at least 8 wk

Trial	Change of effect score from baseline									
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Ichihara et al (2015) [50]	Tamsulosin 0.2 mg/d tOABSS:–0.87, IPSS:–0.26, QoLi:–0.05, PVR: 3.9 ml	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg/d + mirabegron 50 mg/d tOABSS:–2.21, IPSS:–2.34, QoLi:–0.76, PVR: 373 ml Significant vs baseline vs tamsulosin alone	–	–	–	–	–

BPO = benign prostatic obstruction; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; OAB = overactive bladder; OABSS = OAB symptom score; PVR = postvoid residual; Qmax = maximum urinary flow rate; QoL = quality of life; SD = standard deviation.

treatment of BPH/LUTS. Although the effect of combination treatment on LUTS scores did not reach statistically significant levels (IPSS, QoL, Qmax, PV, and PVR), the authors reported a significant difference for the IIEF between the combination therapy and alfuzosin alone (22.9 vs 16.8, $p < 0.001$) [53]. Sildenafil has further been investigated by Sharifi et al. [54] for the management of AUR. No significant difference was noted between the tamsulosin 0.4 mg + sildenafil 50 mg group and the tamsulosin 0.4 mg + placebo group regarding the rate of repeated AUR at 1- and 3-mo follow-up period ($p = 0.07$ and $p = 0.45$, respectively) [54].

Lee et al. [55] evaluated the add-on combination of tadalafil 5 mg/d in 158 patients with erectile dysfunction who were receiving concomitant α-blocker therapy for BPH. IPSS and IIEF-5 scores improved significantly, but Qmax and PVR volume did not. Although the number of patients was scarce, the authors stated that tadalafil 5 mg/d + α-blocker therapy can improve LUTS and restore sexual function [55]. Urodynamic effects of the combination of tamsulosin and daily tadalafil in 40 men with BPH/LUTS were described by Regadas et al. [56]. EOT urodynamics were performed. The PdetQmax showed a significant reduction in the tamsulosin/tadalafil group compared with the tamsulosin/placebo group (13 ± 17 vs -1.2 ± 14, $p = 0.03$). Qmax increased in both groups (tamsulosin/tadalafil and tamsulosin/placebo), but the difference was not significant (1 ± 2.4 vs 1.4 ± 2.4 ml/s). Total IPSS, storage, and voiding subscores improved significantly in the tamsulosin/tadalafil group compared with the tamsulosin/placebo group, leading to the conclusion that the association could reduce detrusor pressure at maximum flow without changing the maximum flow rate during micturition [56]. These results were aligned to those on alfuzosin reported by Kumar et al. [57]. in 2014. Men ($n = 75$) were randomized to receive alfuzosin 10 mg/d, tadalafil 10 mg/d, or the combination of both for 12 wk. Improvements in all IPSS, Qmax, IPSS-QoL, and EDS from baseline to 3 mo were reported in all the three groups (IPSS: 12.3 ± 2.8 vs alfuzosin 9.5 ± 3.5 vs tadalafil 6.3 ± 1.5; Qmax: 4.1 ± 1.4 vs alfuzosin 3.6 ± 1.9 vs tadalafil 1.9 ± 2; IPSS-QoL: 3.8 ± 0.2 vs alfuzosin 3.2 ± 0.9 vs tadalafil 2.4 ± 0.7; EDS: 4.3 ± 3.4 vs alfuzosin 1.8 ± 1.7 vs tadalafil 3.2 ± 2.6). Combination therapy was similar to alfuzosin regarding improvement in Qmax ($p = 0.22$), similar to tadalafil in improvement on erectile function ($p = 0.22$), and better than each monotherapy in improving the IPSS-QoL ($p \leq 0.015$) [57]. Singh et al. [58] further investigated the tamsulosin/tadalafil combination therapy randomizing 133 men: tamsulosin 0.4 mg/d alone, tadalafil 10 mg/d, and combination therapy (tamsulosin + tadalafil). A significant improvement in IPSS, IIEF-5, Qmax, and QoL was observed in all the three groups. A decrease in PVR was also observed. The authors concluded that the improvement in patients with LUTS/BPH was better with combination therapy compared with the single agent alone [58].

The only study on vardenafil was performed by Gacci et al. [59], who compared the safety and efficacy of tamsulosin 0.4 mg/d versus tamsulosin 0.4 mg/d

Table 7 – Men: alpha-blockers and desmopressin combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Bae et al (2013) [51]	1b	2009–2011	208/208	α-Blocker + desmopressin 0.1–0.2 mg	24 wk	IPSS, FVC	65.4 ± 7.8 yr	≥50 with LUTS most likely secondary to BPO. Qmax <15 ml/s, nocturia (≥2 voids per night) and a total IPSS of ≥14 (voiding subscore of ≥8 and storage subscore of ≥6) were treated with an α-blocker for at least 4 wk
Ahmed et al (2015) [52]	1b	2011–2014	248/248	Tamsulosin OCAS 0.4 mg/d + desmopressin (MELT) 60 μg/d	12 wk	Change from baseline to EOT in mean number of nocturnal voids, IPSS	70.14 ± 9.27 yr 45.71 ± 15.34 ml	LUTS/BPH patients, aged ≥50 yr with nocturia (≥2 voids per night) with or without nocturnal polyuria

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Bae et al (2013) [51]	NA	NA	NA	NA	NA	NA	α-Blocker + desmopressin 0.1–0.2 mg IPSS storage: 1.5, FVC Nocturia no. for 3 d:–1.3, nocturnal urine volume (ml): -291 Significant vs baseline	–	–	–	–	–
Ahmed et al (2015) [52]	Tamsulosin OCAS 0.4 mg/d Number of nocturnal voids:–1.41, IPSS: 6.75	NA	NA	NA	NA	NA	Tamsulosin OCAS 0.4 mg/d + desmopressin (MELT) 60 μg/d Number of nocturnal voids:–1.96 [a], IPSS:–6.94	–	–	–	–	–

BPH = benign prostatic hyperplasia; BPO = benign prostatic obstruction; EOT = end of treatment; FVC = frequency-volume chart; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; OCAS = oral controlled absorption system; Qmax = maximum urinary flow rate; SD = standard deviation.

[a] Significant vs tamsulosin alone.

+ vardenafil 10 mg/d. The results showed a between-group significant difference from baseline to 12 wk in Qmax (placebo: +0.07, vardenafil: +2.56), irritative-IPSS subscores (placebo:–1.67, vardenafil:–3.11), and IIEF (placebo: +0.06, vardenafil), leading to the conclusion that the combination approach was well tolerated and more effective than tamsulosin alone [59].

3.1.8.1. Comment. Despite only tadalafil 5 mg being licensed in the context of LUTS management, data on combinations of PDE5Is and other LUTS medications are emerging. Combination of PDE5Is (tadalafil and vardenafil) and α-blockers showed that combination therapy significantly improved IPSS, IIEF score, and Qmax compared with α-blockers alone [12]. All the reported RCTs have the limitation of a short-term follow-up and small sample sizes (Table 8).

3.1.9. Combination of 5-ARIs and PDE5Is

Casabé et al. [60] recently published their findings for combination therapy with tadalafil and finasteride; 659 men were randomized into two groups for a 26-wk study. Three hundred and fifty patients were on finasteride and placebo therapy, while another 345 patients were administered combination therapy of tadalafil and finasteride. IPSS at 4, 12, and 26 wk decreased significantly for the combination group. In addition, combination therapy with tadalafil improved the IIEF-5 at all visits, favoring tadalafil/finasteride coadministration [60]. A subsequent post hoc analysis was performed on the minimal clinically important differences in IPSS, and a prespecified van Elteren analysis was performed for treatment satisfaction based on the Treatment Satisfaction Scale—Benign Prostatic Hyperplasia. At weeks 4, 12, and 26, the proportions of tadalafil/finasteride responders were 57.0%, 68.8%, and 71.4%, respectively, and the proportions of placebo/finasteride responders were 47.9%, 60.7%, and 70.2%, respectively, when defining responders as those who displayed at least a three-point decrease in total IPSS. Alternatively, when responders were defined as those who displayed at least a 25% decrease in total IPSS, the proportions of tadalafil/finasteride responders were 44.8%, 55.5%, and 62.0%, respectively, for the three time points and 32.9%, 51.9%, and 58.3%, respectively, for the placebo/finasteride group. Odds ratio of IPSS decrease of at least three points was statistically significant in favor of tadalafil/finasteride at weeks 4 and 12, but not at week 26. These data further supported the utility of coadministration of tadalafil for early symptom improvement in men starting treatment with a 5-ARI [61].

3.1.9.1. Comment. These two studies were randomized and properly powered, highlighting significant results in patients with LUTS and ED (Table 9).

3.1.10. Combination of α1-blocker and phytotherapy

Only two RCTs were identified about the combination of saw palmetto with tamsulosin. In 2014, the PROCOMB trial evaluated the efficacy and tolerability of combination therapy between *Serenoa repens* (SeR), lycopene (Ly), and selenium (Se) + tamsulosin versus single therapies [62]. A total of 225 patients were randomized: group A (SeR-Se-Ly), group B (tamsulosin 0.4 mg), and group C (SeR-Se-Ly-tamsulosin 0.4 mg). The percentage change of IPSS was significantly greater for combination therapy versus tamsulosin (18.2% vs 13.8%, $p < 0.05$) and versus SeR-Se-Ly (18.2% vs 14.3%, $p < 0.05$). The percentage increase of Qmax for group C was greater than that for group A (24.0 vs 15.4, $p < 0.05$) but not greater that for group B (24.0 vs 17.4, $p = 0.15$) [62]. Ryu et al. [63] compared the efficacy and safety of SeR plus tamsulosin with tamsulosin only over 12 mo in 140 men with symptomatic BPH. Patients were randomly assigned either to tamsulosin 0.2 mg/d plus SeR320 mg/d or to tamsulosin 0.2 mg/d only. At 12 mo, total IPSS decreased similarly between tamsulosin + SeR and tamsulosin. The storage symptoms improved significantly more with tamsulosin + SeR (–1.7 vs–0.8 with tamsulosin alone) and lasted at 12 mo. The changes of voiding subscore, LUTS QoL, Qmax, PVR, PSA, and PV showed no significant differences between the groups [63].

3.1.10.1. Comment. According to the EAU guidelines, only two RCTs are adequately powered and homogeneous for the plant extract technique [12]. In general, no phytotherapeutic agent has been shown to reduce prostate size, and no trial has proved a reduction of BOO or a decrease in disease progression [12]. Although these studies reported promising results for combination therapy, the value of saw palmetto in the treatment of LUTS remains ambiguous (Table 10) [64].

3.2. Women: combination drug therapy for non-neurogenic LUTS

Our literature search led to 18 papers published from January 1988 to December 2017 for women (Fig. 2 and Supplementary Table 2).

3.2.1. Combination of antimuscarinics and adrenergic β3 receptor agonists

The literature search led to eight papers on the combination of solifenacin and mirabegron. All the studies are characterized by a mixed population of men and women. Details have previously been discussed in the men section and will be reported briefly herein given the majority of female patients in most of the trials.

The MILAI study showed significant improvements in 183 women with OAB symptoms with a combination therapy of mirabegron and solifenacin from baseline to EOT [27]. The Symphony study confirmed these results in 439 women who significantly improved on MVV, micturition frequency, urgency, HRQoL, and PROs compared with placebo and solifenacin 5 mg monotherapy with similar safety and acceptability [28,29]. Kosilov et al. [30] reported their experience in 137 elderly women treated with standard doses of solifenacin and mirabegron, providing satisfactory therapeutic effect and an improvement in QoL and self-esteem of patients. The BESIDE study enrolled 1821 OAB women remaining incontinent despite daily solifenacin 5 mg, who were treated with solifenacin 5 or

Table 8 – Men: alpha-blocker and PDE5I combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Ozturk et al (2012)	1b	NR	100/100	Alfuzosin XL 10 mg + sildenafil 50 mg	12 wk	IPSS, IIEF-6, QoL, Qmax, PVR	60.2 ± 17.8 yr	> 45 yr, naïve to any type of LUTS and ED treatment, IPSS ≥12, QoL ≥3
Lee et al (2012) [55]	1b	2009–2010	119/119	Tamsulosin 0.2 mg or alfuzosin 10 mg + tadalafil 5 mg/d	12 wk	IPSS, PVR, Qmax, QoL, IIEF-5	58.02 ± 7.70 yr	Men, 40 and 70 yr of age, IIEF-5 score of <18 on screening, were willing and able to participate in this clinical study, LUTS/BPH treated with α-blocker at least for 3 mo
Regadas et al (2013) [56]	1b	2010–2011	40/40	Tamsulosin 0.4 mg + tadalafil 5 mg/d	4 wk	PdetQmax, Qmax	61.6 ± 1.7 yr 44.3 ±1.8 ml	Men at least 45 yr old complaining for BPH/LUTS, bladder outlet obstruction index >20 and IPSS >14
Gacci et al (2012) [59]	1b	NR	60/60	Tamsulosin 0.4 mg/d + vardenafil 10 mg/d	12 wk	IPSS, OAB-q SF, IIEF-5	66.3 ± 6.0 yr	Men, age 40–80 yr, IPSS ≥12, OAB-q SF≥ 8, voided volume <400 ml, maximum flow rate >5 ml/s (with a voided volume of >150 ml)
Kumar et al (2014) [57]	1b	NR	75/75	Alfuzosin 10 mg/d + tadalafil 10 mg/d	12 wk	IPSS, Qmax, PVR, EDS	62.6 ± 7.9 yr 39.2 ± 16.6 ml	Men >50 yr, IPSS ≥8
Singh et al (2014) [58]	1b	2010–2012	133/133	Tamsulosin 0.4 mg/d + tadalafil 10 mg/d	12 wk	IPSS, IPSS QoL index, Qmax, PVR, IIEF-5	61.61 ± 6.9 yr	Men, ≥45 yr, LUTS/BPH of ≥6 mo, IPSS >8, PSA ≤4.0 ng/ml, Qmax >5 and <15 ml/s with minimum voided volume of >125 ml at screening
Sharifi et al (2014) [54]	1b	2009–2012	101/101	Tamsulosin 0.4 mg/d + sildenafil 50 mg/d	12 wk	TWOC at 24 h, 7 d, and 3 mo after the first episode of spontaneous AUR	59.64 ± 3.84 yr 54.86 ± 19.21 ml	Men, <65 yr, initial episode of spontaneous AUR

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Ozturk et al (2012)	Alfuzosin XL 10 mg IPSS:−5.1, IIEF-6: 1.9, QoL:−1.86, Qmax: +3.2, PVR:−12.8	NA	NA	NA	NA	NA	Alfuzosin XL 10 mg + sildenafil 50 mg IPSS:−5.8, IIEF-6: 7.8, QoL:−1.8, Qmax: 3.4, PVR:−14.1 Only IIEF-6 significant vs monotherapy	–	–	–	–	–
Lee et al (2012) [55]	NA	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg or alfuzosin 10 mg + tadalafil 5 mg/d IPSS:−8.24, PVR:−2.45, Qmax:−0.08, QoL: 0.08, IIEF-5: 7.23 Significant for IPSS, QoL, and IIEF5 vs baseline	–	–	–	–	–

Table 8 (*Continued*)

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Regadas et al (2013) [56]	Tamsulosin 0.4 mg/placebo PdetQmax:–1.22, Qmax: 1.22, IPSS:–6	NA	NA	NA	NA	NA	Tamsulosin 0.4 mg + tadalafil 5 mg/d PdetQmax:–13, Qmax: 1.05, IPSS:–9.75 Significant for PdetQmax and IPSS, vs tamsulosin + placebo	–	–	–	–	–
Gacci et al (2012) [59]	Tamsulosin 0.4 mg/d + placebo IPSS:–3.7, OAB-q SF:–2.8, IIEF-5: 0.1	NA	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + vardenafil 10 mg/d IPSS:–5.8, OAB-q SF:–4.5, IIEF-5: 2.6 Significant vs placebo	–	–	–	–	–
Kumar et al (2014) [57]	Alfuzosin 10 mg/d IPSS:–9.5, Qmax: 2.9, PVR:–22.8, EDS: 2.3	Tadalafil 10 mg/d IPSS:–6.3, Qmax: 1.6, PVR:–13.8, EDS: 3.3	NA	NA	NA	NA	Alfuzosin 10 mg/d + tadalafil 10 mg/d IPSS:–12.2, Qmax: 4.1, PVR:–56.2, EDS: 4.3 Significant vs baseline and vs monotherapy	–	–	–	–	–
Singh et al (2014) [58]	Tamsulosin 0.4 mg/d IPSS:–10.67, IPSS QoL:–4.11, Qmax: 3.11, PVR: 48.18, IIEF-5: 3.96	Tadalafil 10 mg/d IPSS:–6.83, IPSS QoL index:–4.04, Qmax: 2.63, PVR: 48.92, IIEF-5: 5.5	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + tadalafil 10 mg/d IPSS:–6.39, IPSS QoL index:–4.5, Qmax: 3.66, PVR: 79.54, IIEF-5: 6.39 Not significant vs monotherapy alone	–	–	–	–	–
Sharifi et al (2014) [54]	Tamsulosin 0.4 mg/d + placebo TWOC at 24 h: 72.5%; 7 d: 62.7%; 3 mo: 47%	NA	NA	NA	NA	NA	Tamsulosin 0.4 mg/d + sildenafil 50 mg/d TWOC at 24 h: 82%; 7 d: 70%; 3 mo: 52% Significant vs monotherapy at 24 h	–	–	–	–	–

AUR = acute urinary retention; BPH = benign prostatic hyperplasia; ED = erectile dysfunction; EDS = erectile dysfunction score; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; PDE5I = phosphodiesterase type 5 inhibitor; Qmax = maximum urinary flow rate; PVR = postvoid residual; QoL = quality of life; SD = standard deviation; TWOC = trial without catheter.

Table 9 – Men: 5-ARI and PDE5I combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Casabé et al (2014) [60]	1b	2010–2012	659/659	Tadalafil 5 mg/d + finasteride 5 mg/d	26 wk	IPSS, IIEF-5	63.7 ± 7.7 yr 49.4 ± 20.4 ml	Men, ≥45 yr, BPH LUTS for >6 mo, prostate volume ≥30 ml, IPSS total score ≥13, Qmax 4–15 ml/s and were naïve to 5-ARI therapy
Roehrborn et al (2015) [61]	1b	NR	695/695	Tadalafil 5 mg/d+ finasteride 5 mg/d	26 wk	TSS-BPH	63.7 ± 7.7 yr 49.4 ± 20.4 ml	Men aged ≥45 yr with BPH LUTS for >6 mo, prostate volume ≥30 ml, IPSS total score ≥13, and were naïve to 5-ARI therapy

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Casabé et al (2014) [60]	Finasteride 5 mg/d + placebo IPSS:–4.5, IIEF-5: 0	NA	NA	NA	NA	NA	Tadalafil 5 mg/d + finasteride 5 mg/d IPSS:–5.5, IIEF-5: 4.7 Significant vs monotherapy	–	–	–	–	–
Roehrborn et al (2015) [61]	Finasteride 5 mg/d + placebo TSS-BPH: 2.0 ± 0.63	NA	NA	NA	NA	NA	Tadalafil 5 mg/d + finasteride 5 mg/d TSS-BPH: 2.1 ± 0.66 Significant vs monotherapy	–	–	–	–	–

5-ARI = 5α-reductase inhibitor; BPH = benign prostatic hyperplasia; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; PDE5I = phosphodiesterase type 5 inhibitor; Qmax = maximum urinary flow rate; SD = standard deviation; TSS-BPH = Treatment Satisfaction Scale BPH.

Table 10 – Men: alpha-blocker and phytotherapy combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (male/total)	Drugs' combination (dose)	Trial duration	Primary endpoint	Age of patients and size of prostate at baseline (mean ± SD)	Inclusion criteria
Morgia et al (2014) [62]	1b	2011–2012	219/219	SeR-Se-Ly + tamsulosin 0.4 mg	52 wk	IPSS, PVR, Qmax	65 ± NR yr 45 ± NR ml	Age between 55 and 80 yr, digital rectal examination negative for prostate nodules, PSA <4 ng/ml, IPSS ≥12, prostate volume <60 cc (assessed by ultrasound), Qmax <15 ml/s, PVR urine <150 ml
Ryu et al (2015) [63]	1b	2012–2013	103/103	Tamsulosin 0.2 mg/d + SerR 320 mg/d	52 wk	IPSS, PVR, Qmax. QoL	62.5 ± 1.21 yr 30.1 ± 0.93 ml	Men ≥50, IPSS >10. Qmax of 5–15 ml/s for voided volume of at least 150 ml with a postvoiding volume of <150 ml, PV of at least 25 cc, and PSA <4 ng/ml

Trial	Change of effect score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Morgia et al (2014) [62]	SeR-Se-Ly IPSS:–3, PVR:–10, Qmax: +2.	Tamsulosin 0.4 mg/d IPSS:–3, PVR:–30, Qmax: +2	NA	NA	NA	NA	SeR-Se-Ly + tamsulosin 0.4 mg IPSS:–4, PVR:–34.5, Qmax: +2.3 Significant vs monotherapy	–	–	–	–	–
Ryu et al (2015) [63]	Tamsulosin 0.2 mg/d IPSS:–5.5, PVR:–10.6, Qmax: 2, QoL: 2.5, storage IPSS:–0.9	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg/d + SeR 320 mg/d IPSS:–5.8, PVR:–8.3, Qmax: 2.1, QoL: 2.4, storage IPSS:–1.9 Significant only for storage IPSS vs tamsulosin alone	–	–	–	–	–

IPSS = International Prostate Symptom Score; LoE = level of evidence; Ly = lycopene; NA = not available; NR = not reported; PSA = prostate-specific antigen; PV = prostate volume; PVR = postvoid residual; Qmax = maximum urinary flow rate; QoL = quality of life; SD = standard deviation; Se = selenium; SeR = *S. repens*.

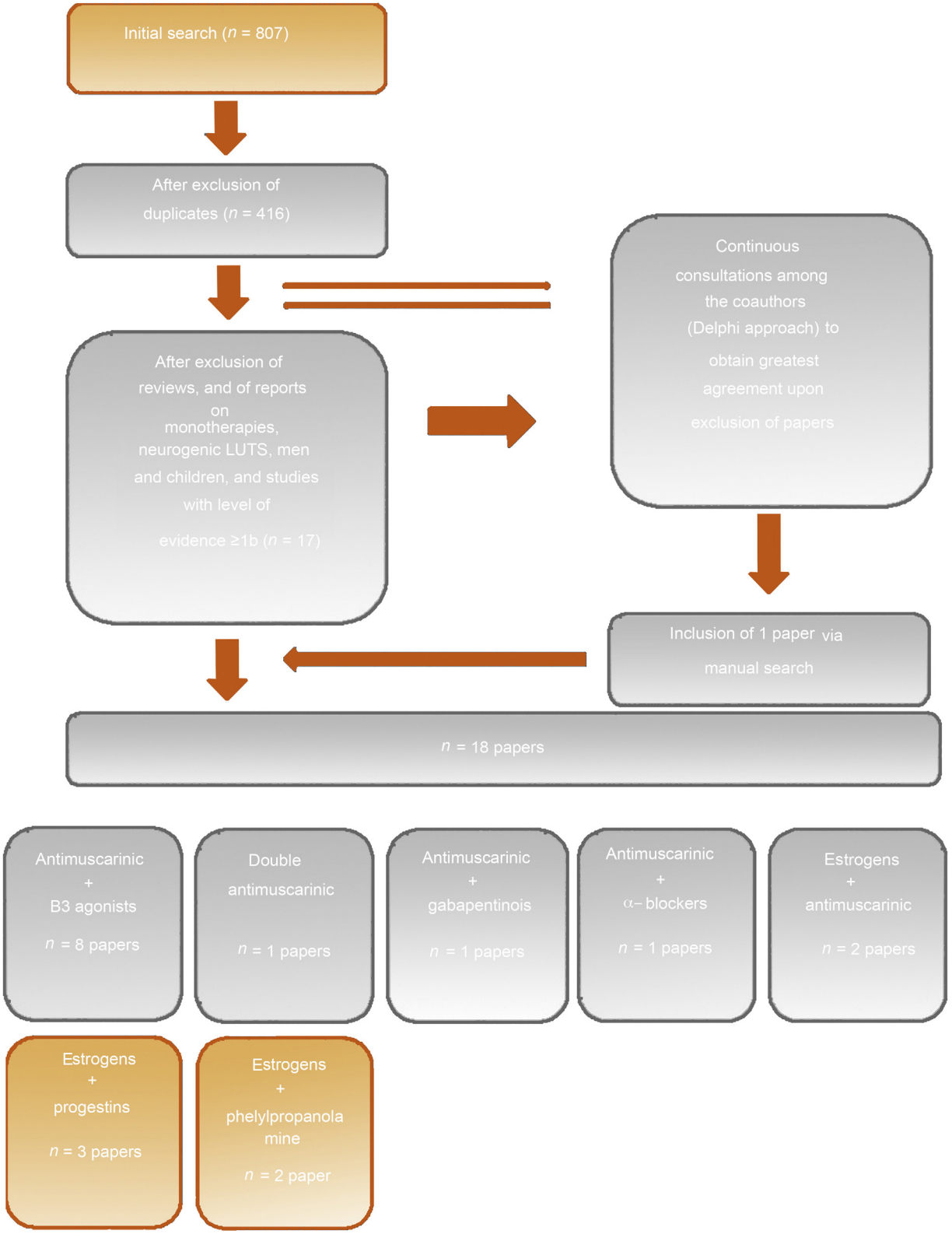

Fig. 2 – PRISMA "female" flow chart. LUTS = lower urinary tract symptoms; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

10 mg and mirabegron 50 mg. At EOT, combination was superior to solifenacin 5 mg, with significant improvements in daily incontinence ($p = 0.001$), daily micturitions ($p < 0.001$), incontinence noted in a 3-d diary ($p = 0.014$), and OAB-5D [31–35]. The SYNERGY study enrolled 2615 women with OAB and UI. The authors concluded that solifenacin 5 mg + mirabegron 25 or 50 mg provided a consistent additive effect by week 4 of treatment,

improving UI episodes/24 h, micturitions/24 h, MVV/micturition, and nocturia episodes/24 h [36]. A post hoc analysis also showed that the combination therapy had an additive effect for many HRQoL parameters, including OAB-q symptom bother score, HRQoL total score, and PPBC [37].

3.2.1.1. Comment. In all these RCTs, combination therapy demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, UUI, and urgency, and also patient perception of treatment benefit. As we mentioned above in the men section, these studies had a predominantly female study population, but they did not report the results separately for the genders. This statistical issue could have influenced the statistical significance of the results leading to less clinical meaningful data. Safety data could have been underpowered. Studies were rarely powered for safety outcomes (Table 11).

3.2.2. Combination of antimuscarinics (double antimuscarinic combination therapy)

Kosilov et al. [38] investigated the role of combination of solifenacin and trospium in 98 OAB elderly women. Low-dose trospium 15 mg/d and solifenacin 5 mg/d provided good clinical and urodynamic effects in terms of reflex volume, bladder capacity, and detrusor compliance and a decrease in the frequency of urination and urinary urgencies. It is advisable that the appropriate dosing is an important issue when adding two drugs with a similar mechanism of action. This RCT has been further described in the men section.

3.2.2.1. Comment. Although a predominant female population, the limitation of this study is that the mix-gender approach may be adequately powered for effects in the overall group and not for effects within each gender probably limiting the clinical relevance. Safety data could have been underpowered (Table 12).

3.2.3. Combination of antimuscarinics and Gabapentinoids

Gabapentinoids, such as pregabalin, are $\alpha 2\delta$ subunit modifiers that affect GABA transport. Pregabalin increases the density of GABA transporter proteins and increases the rate of functional GABA transport. Marencak et al. [65] assessed the efficacy and safety of pregabalin alone or in combination with tolterodine extended release in women with idiopathic OAB. The study enrolled 178 women with OAB, reporting more than eight micturitions/24 h and more than four urgency episodes/wk on 5-d bladder diary at baseline. Individuals were randomized to standard-dose pregabalin/tolterodine (150 mg b.i.d./4 mg once daily), pregabalin alone (150 mg b.i.d.), tolterodine (4 mg die), low-dose pregabalin/tolterodine (75 mg b.i.d./2 mg once daily), and placebo. Baseline-adjusted changes in the primary endpoint MVV were significantly higher after treatment with standard-dose pregabalin/tolterodine (39.5 ml) versus tolterodine alone (15.5 ml; $p < 0.0001$), and with pregabalin alone (27.4 ml) versus tolterodine alone ($p = 0.005$) and placebo (11.9 ml; $p = 0.0006$). Treatments were generally well tolerated. Dry mouth and dizziness were the most frequently reported, the majority occurring during treatment with pregabalin alone or standard-dose pregabalin/tolterodine [65].

3.2.3.1. Comment. Pregabalin, alone or with tolterodine, may offer an alternative treatment option for idiopathic OAB in women even if further studies are mandatory to assess a potential synergism of this combination in treating idiopathic OAB. The limitations of the study include the short duration of the studies and the short follow-up period (Table 13).

3.2.4. Combination of antimuscarinics and $\alpha 1$-blockers

In 2011, Kim et al. [66] assessed the effect of tamsulosin 0.2 mg with or without tolterodine 2 mg on female patients with a Qmax of <12 ml/s who were suspected of having a functional BOO. Patients were randomly assigned to treatment with tamsulosin alone (0.2 mg/d, group I) or tamsulosin combined with tolterodine extended release (2 mg/d, group II) once daily. The primary endpoint was the change from baseline and after 12 wk of treatment in the IPSS-QoL score. The secondary endpoint was the change from baseline in Qmax and PVR. After 12 wk of treatment, there were no significant differences in subjective symptom scores or objective uroflowmetric parameters between the two groups except for storage symptoms (group I, 4.3 ± 1.6 vs group II, 3.8 ± 0.9) and PVR urine (group I, 31.8 ± 22.4 ml vs group II, 56.1 ± 29.7 ml). The overall incidence of adverse events was 8.4% in group I and 29% in group II ($p < 0.05$). The major adverse events in group II were dry mouth (10.7%) and constipation (6.7%). No AUR occurred in either group. Combination therapy improved storage symptoms. However, women with a slight degree of storage symptoms need to be accurately evaluated before prescribing anticholinergics [66].

3.2.4.1. Comment. The number of patients included in the study was very small. The study did not have a placebo control group. The tamsulosin dose of 0.2 mg may lead to difficult interpretation of the results. Appropriate dosing is important when adding two drugs (Table 14).

3.2.5. Combination of antimuscarinics and estrogens

Only two RCTs were identified about the combination of antimuscarinics and estrogens. Each of the studies described the use of vaginal estrogen cream.

Serati et al. [67] were the first group to investigate whether the administration of local estrogens in addition to antimuscarinics could have a synergistic effect in the therapy of OAB. Postmenopausal women ($n = 229$) with symptomatic urodynamically proven detrusor overactivity were prospectively enrolled and divided into two groups. Women in group 1 ($n = 129$) were prescribed tolterodine 4 mg once daily; women in group 2 ($n = 100$) were prescribed both tolterodine 4 mg and concomitant estriol cream application once daily. After 12 wk of treatment, the two groups were compared in terms of subjective efficacy for OAB symptom improvement. There was no significant difference between the two groups in terms of efficacy of

Table 11 – Women: antimuscarinic and beta-3 agonist combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
SYNERGY Robinson et al (2017) [37]	1b	NR	2615/3398	Solifenacin 5 mg + mirabegron (25 or 50 mg)	18 wk	Change from baseline to EOT in HRQoL (OABq) and PROs (PPBC) and TS-VAS	57.4 ± 13.4	≥18 yr with wet OAB for ≥3 mo who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-d micturition diary
SYNERGY Herschorn et al (2017) [36]	1b	NR	2615/3398	Solifenacin 5 mg + mirabegron (25 or 50 mg)	18 wk	Change from baseline to EOT in the mean number of UI episodes/24 h and micturitions/24 h	57.4 ± 13.4	≥18 yr with wet OAB for ≥3 mo who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-d micturition diary
BESIDE Herdman et al (2017) [32]	1b	NR	1821/2174	Solifenacin 5 mg + mirabegron 50 mg	20 wk	Change from baseline to EOT in the EQ-5D-5L and OAB-5D	57 ± 13.2 yr PV NR	≥18 yr with OAB for ≥3 mo who recorded ≥2 UI episodes/24 h. After 4 wk of single-blind daily solifenacin 5 mg, patients remaining incontinent at baseline were randomized
BESIDE Drake et al (2016) [31]	1b	NR	1821/2174	Solifenacin 5 mg + mirabegron 50 mg	20 wk	Change from baseline to EOT in the mean number of UI episodes/24 h	57 ± 13.2	≥18 yr with OAB for ≥3 mo who recorded ≥2 UI episodes/24 h. After 4 wk of single-blind daily solifenacin 5 mg, patients remaining incontinent at baseline were randomized
Symphony Abrams et al (2017) [29]	1b	2013	439/1306	Solifenacin (2.5, 5, 10 mg) + mirabegron (25 and 50 mg)	12 wk	Change from baseline to EOT in HRQoL (OABq) and PROs (PPBC)	54.6 ± 13.4	≥18 yr with symptoms of OAB for 3 mo. ≥8 micturitions per 24 h, ≥1 urgency episode/24 h (with or without incontinence), based on a 3-d electronic patient micturition diary
Symphony Abrams et al (2015) [28]	1b	2013	439/1306	Solifenacin (2.5 and 5 mg) + mirabegron (25 and 50 mg)	12 wk	Change from baseline to EOT in MVV	54.1 ± 14.1	≥18 yr with symptoms of OAB for 3 mo. ≥8 micturitions per 24 h, ≥1 urgency episode/24 h (with or without incontinence), based on a 3-d electronic patient micturition diary
MILAI Yamaguchi et al (2015) [27]	1b	2014	183/218	Solifenacin (2.5 and 5 mg) + mirabegron (25 and 50 mg)	18 wk	Changes from baseline in OABSS total score, OAB-q SF score, mean number of micturitions/24 h, mean number of urgency episodes/24 h, mean number of UI episodes/24 h, mean number of urgency UI episodes/24 h, MVV, and mean number of nocturia episodes/night	64.6 ± 9.97	≥20 yr with OAB, previously treated with solifenacin at a stable dose of 2.5 or 5 mg once daily for at least 4 wk. OABSS total score of ≥3 points and a question 3 OABSS score of ≥2 points

Table 11 (*Continued*)

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Kosilov et al (2015) [30]	1b	NR	137/232	Solifenacin 10 mg + mirabegron 50 mg	6 wk	Change from baseline to EOT in MVV, PVR, episodes of incontinence and micturitions	71.2	≥65 yr, who suffer from severe symptoms of OAB (episodes of incontinence ≥3/d)

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
SYNERGY Robinson et al (2017) [37]	Solifenacin 5 mg HRQoL: +22.7 Significant vs placebo PPBC:−1.3 Significant vs placebo TS-VAS: 2.3 Significant vs placebo	Mirabegron 25 mg HRQoL: +21.6 Significant vs placebo PPBC:−1.2 Significant vs placebo TS-VAS: 2.2 Significant vs placebo	Mirabegron 50 mg HRQoL: +23.1 Significant vs placebo PPBC:−1.3 Significant vs placebo TS-VAS: 2.2 Significant vs placebo	–	–	HRQoL: +17 PPBC:−0.9 TS-VAS: 1.4	Solifenacin 5 mg/ mirabegron 25 mg HRQoL: +26.9 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 PPBC:−1.5 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 TS-VAS: 2.5 Significant vs placebo, vs mirabegron 25, not vs solif 5 mg	Solifenacin 5 mg/ mirabegron 50 mg HRQoL: +27.5 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 50 PPBC:−1.7 Significant vs placebo, vs solifenacin 5 mg, vs mirabegron 25 TS-VAS: 2.6 Significant vs placebo, not vs mirabegron 25, not vs solif 5 mg	–	–	–	–
SYNERGY Herschorn et al (2017) [36]	Solifenacin 5 mg Zero UI/24 h: 177, not significant vs placebo Frequency normalization: 186, significant vs placebo	Mirabegron 25 mg Zero UI/24 h: 166, not significant vs placebo Frequency normalization: 172, significant vs placebo	Mirabegron 50 mg Zero UI/24 h: 188, significant vs placebo Frequency normalization: 163, significant vs placebo	–	–	Zero UI/24 h: 155 Frequency normalization: 128	Solifenacin 5 mg + mirabegron 25 mg Zero UI/24 h: 417, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg Frequency normalization: 422, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg	Solifenacin 5 mg + mirabegron 50 mg Zero UI/24 h: 426, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg Frequency normalization: 429, significant vs placebo, vs mirabegron 25 mg and vs solif 5 mg	–	–	–	–
BESIDE Herdman et al (2017) [32]	Solifenacin 5 mg EQ-5D-5L: 0.040 OAB-5D: 0.085	Solifenacin 10 mg EQ-5D-5L: 0.044 OAB-5D: 0.087	–	–	–	–	Solifenacin 5 mg + mirabegron 50 mg EQ-5D-5L: 0.059 OAB-5D: 0.107 Significant vs solifenacin 5 mg and vs solifenacin 10 mg	–	–	–	–	–
BESIDE Drake et al (2016) [31]	Solifenacin 5 mg UI/24 h:−1.54	Solifenacin 10 mg UI/24 h:−1.63	–	–	–	–	Solifenacin 5 mg + mirabegron 50 mg UI/24 h:−1.82 Significant vs solifenacin 5 mg and vs solifenacin 10 mg	–	–	–	–	–

Table 11 (*Continued*)

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Symphony Abrams et al (2017) [29]	Solifenacin 2.5 mg HRQoL: +2.6 Not significant vs placebo PPBC: +3.1 Not significant vs placebo	Solifenacin 5 mg HRQoL:–0.3 Not significant vs placebo PPBC:–1.3 Not significant vs placebo	Solifenacin 10 mg HRQoL: +23.5 Not significant vs placebo and solif 5 mg PPBC:–1.5 Not significant vs placebo and solif 5 mg	Mirabegron 25 mg HRQoL: +20.2 Not significant vs placebo PPBC:–1.4 Not significant vs placebo	Mirabegron 50 mg HRQoL: +23.1 Not significant vs placebo PPBC:–1.5 Not significant vs placebo	HRQoL: +22 PPBC:–1.4	Solifenacin 2.5 mg/ mirabegron 25 mg HRQoL: +22.7 Not significant vs placebo, not significant vs solifenacin 5 mg alone PPBC:	Solifenacin 2.5 mg/ mirabegron 50 mg HRQoL: +22.7 Not significant vs placebo, not significant vs solifenacin 5 mg alone PPBC:–1.4 Not significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg HRQoL: +26 Not significant vs placebo, significant vs solifenacin 5 mg alone PPBC:–1.7 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg HRQoL: +28.4 Significant vs placebo and vs solifenacin 5 mg alone PPBC:–1.8 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 25 mg HRQoL: +27.4 Significant vs placebo and vs solifenacin 5 mg alone PPBC:–1.8 Significant vs placebo and vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 50 mg HRQoL: +27 Not significant vs placebo, significant vs solifenacin 5 mg alone PPBC:–1.6 Not significant vs placebo, not significant vs solifenacin 5 mg alone
Symphony Abrams et al (2015) [28]	Solifenacin 2.5 mg +36.4 ml Significant vs placebo	Solifenacin 5 mg +36 ml Significant vs placebo	Solifenacin 10 mg +36.2 ml Significant vs placebo but not significant vs solifenacin 5 mg alone	Mirabegron 25 mg +25 ml Not significant vs placebo	Mirabegron 50 mg +35 ml Significant vs placebo	+14 ml	Solifenacin 2.5 mg/ mirabegron 25 mg +39.4 ml Significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 2.5 mg/ mirabegron 50 mg +42 ml Significant vs placebo, not significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg +54 ml Significant vs placebo, vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg +54.2 ml Significant vs placebo, vs solifenacin 5 mg alone	Solifenacin 10 mg/ mirabegron 25 mg +58 ml Significant vs placebo, vs solifenacin 5 mg alone	
							Solifenacin10 mg/ mirabegron 50 mg +62.3 ml Significant vs placebo, vs solifenacin 5 mg alone					
MILAI Yamaguchi et al (2015) [27]	NA	NA	NA	NA	NA	NA	Solifenacin 2.5 mg/ mirabegron 25 mg +29.8 ml Significant vs solifenacin 5 mg alone	Solifenacin 2.5 mg/ mirabegron 50 mg +33.0 ml Significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 25 mg +34.1 ml Significant vs solifenacin 5 mg alone	Solifenacin 5 mg/ mirabegron 50 mg +36.9 ml Significant vs solifenacin 5 mg alone	–	–
Kosilov et al (2015) [30]	Mirabegron 50 mg/d MVV: +35 ml, PVR: +11.5 ml, EI:–2.3/d, micturitions:–3.7/d Significant before and after treatment	Solifenacin 10 mg/d MVV: +64 ml, PVR: +9 ml, EI:–2.2/d, micturitions:–3.4/d Significant before and after treatment	NA	NA	NA	MVV: +12 ml, PVR:–3 ml Not significant before and after treatment	Solifenacin 10 mg + mirabegron 50 mg MVV: +94 ml, PVR: +10.5 ml, EI:–3.8/d, micturitions:–4/d Significant vs mirabegron alone and vs solifenacin alone	–	–	–	–	–

EI = episodes of incontinence; EOT = end of treatment; HRQoL = health-related quality of life; LoE = level of evidence; MVV = mean voided volume; NA = not available; NR = not reported; OAB = overactive bladder; OABSS = OAB symptom score; PPBC = Patient Perception of Bladder Condition; PRO = patient-reported outcome; PV = prostate volume; PVR = postvoid residual; solif = solifenacin; TS-VAS = Treatment Satisfaction Visual Analogue Scale; UI = urinary incontinence.

Table 12 – Women: double antimuscarinic combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Kosilov et al (2014) [38]	1b	2012	98/177	Trospium 15 mg/d + solifenacin 5 mg/d	16 wk	Change from baseline to EOT in MVV, PVR, episodes of incontinence and micturitions	69.4	Moderate symptoms of OAB who during the previous 5 yr (but not less than half a year before the study) had undergone monotherapy with antimuscarinic drugs with unsatisfactory or short-term and rapidly disappearing effect

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kosilov et al (2014) [38]	NA	NA	Not significant before and after treatment	Trospium 15 mg/d + solifenacin 5 mg/d MVV: +106 ml, PVR: +11 ml, EI:−1.18/d, micturitions:−1.85/d Significant before and after treatment and vs standard dose antimuscarinics	Trospium 30 mg/d + solifenacin 10 mg/d MVV: +94 ml, PVR: +11 ml, EI:−1.08/d, micturitions:−3.59/d Significant before and after treatment	–	–	–	–	–	–	–

EI = episodes of incontinence; EOT = end of treatment; LoE = level of evidence; MVV = mean voided volume; NA = not available; NR = not reported.

Table 13 – Women: antimuscarinic and gabapentinoid combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Marencak et al (2011) [65]	1b	2005–2006	178	Pregabalin/tolterodine ER (150 mg twice daily [b.i.d.]/4 mg once daily	26 wk	MVV (ml) at baseline and week 4 (diary based)	52.9 ± 13.3	Women aged ≥18 yr, frequency ≥8 micturitions/24 h, ≥4 episodes of urgency/wk, MVV <300 ml in a 5-d bladder diary before randomization

Trial	Change of symptom score from baseline										
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Marencak et al (2011) [65]	TER alone (4 mg once daily) +15.5 ml	PGB alone (150 mg twice daily) +27.4 ml Significant vs TER alone, vs placebo	NA	NA	NA	+11.9 ml	PGB/TER (150 mg b.i.d./4 mg once daily) +39.5 ml Significant vs standard-dose TER alone	Low-dose PGB/TER (75 mg b.i.d./2 mg once daily) +20.4 ml	–	–	–	–

ER = extended release; LoE = level of evidence; MVV = mean voided volume; PGB = pregabalin; NA = not available; TER = tolterodine extended release;.

therapy: 80.6% in group 1 versus 82% in group 2 ($p = 0.86$). Therefore, no synergistic effect of local estrogens and antimuscarinics in the treatment of OAB was found [67].

Different results were published by Tseng et al. [68], who underlined that the combination of vaginal estrogen cream and tolterodine is a potential better therapy for postmenopausal women with OAB. Over a period of 11 mo, 80 postmenopausal women with OAB were equally randomized into two groups. The interventions for the 12-wk treatment period included 2 mg tolterodine twice per day for group A and 2 mg tolterodine twice per day/vaginal conjugated equine estrogen 0.625 mg twice a week for group B. Identical pre- and post-treatment assessments included bladder diary, Urogenital Distress Inventory-6 (UDI-6), and Incontinence Impact Questionnaire-7 (IIQ-7). Group B had significant improvements in mean daytime frequency and voided volume after treatment (14.8–5.8 vs 14.1–6.4, $p = 0.001$ and 115.8–141.9 vs 108.5–134.5, $p = 0.007$, respectively). Group B had a statistically significant improvement in QoL than group A in UDI-6 and IIQ-7 (8.6–6.9 vs 9.5–7.2, $p < 0.001$ and 9.4–6.1 vs 10.2–6.5, $p < 0.001$, respectively). Changes in the other symptoms, including nocturia, urgency, and UUI, were not statistically significant [68].

3.2.5.1. Comment. Results obtained from these studies are controversial. The former discouraged the use of estrogens in women with symptomatic detrusor overactivity/OAB; the latter reported promising results for frequency and MVV. No significant adverse effects were observed in both trials even if safety data could have been underpowered. The small sample size and short-term follow-up are limitations in either study. Furthermore, these RCTs are not homogeneous in terms of population and estrogen cream used. Therefore, further studies are mandatory in order to clearly understand the possible synergic effect of estrogens in combination with antimuscarinics in OAB patients (Table 15).

3.2.6. *Combination of estrogens and progestins*

The literature search led to a total of three papers on the combination of estrogens and progestins. The first paper was published in 1998 by Kok et al. [69] with the aim to investigate the role of combined hormone replenishment therapy (HRT) in 95 women with micturition complaints. HRT consisted of 2 mg 17 b-estradiol in combination with 2.5, 5, 10, or 15 mg dydrogesterone, orally once a day. The baseline assessment was done before starting HRT and after 6 mo of treatment. Data were collected focusing on diurnal urinary frequency, nocturnal urinary frequency, and UI. Postmenopausal women reported an improvement after 6 mo of continuous combined HRT. Nocturia disappeared in 65.4% of the women after treatment, and 23.3% reported to be cured of their UI; a trend of improvement in diurnal frequency was also reported ($p = 0.01$) [69].

In 2001, Ouslander et al. [70] randomized 32 female nursing home residents to receive either oral estrogen (0.625 mg) combined with progesterone (2.5 mg) or placebo, daily for 6 mo, to examine the effects on UI and LUTS. Evaluation was done at baseline, and 3 and 6 mo. Results

Table 14 – Women: antimuscarinic and alpha-blocker combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Kim et al (2011) [66]	1b	2007–2008	181	Tamsulosin (0.2 mg/d) or tamsulosin + tolterodine ER (2 mg/d)	12 wk	Change from baseline and after 12 wk of treatment in the IPSS, QoL score, Qmax, and PVR	52.3 ± 5.3 in group I and 53.7 ± 10.8 in group II	Women aged ≥18 yr with LUTS, IPSS >8, Qmax <12 ml/s

Trial	Change of symptom score from baseline										
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kim et al (2011) [66]	Tamsulosin 0.2 mg/d Significant vs baseline	NA	NA	NA	NA	NA	Tamsulosin 0.2 mg/d + tolterodine ER 2 mg/d IPSS, QoL score, Qmax and PVR: significant versus baseline, not significant vs tamsulosin alone. Only storage IPSS significant vs tamsulosin alone	–	–	–	–	–

ER = extended release; IPSS = International Prostate Symptom Score; LoE = level of evidence; LUTS = lower urinary tract symptoms; NA = not available; PVR = postvoid residual; Qmax = maximum urinary flow rate; QoL = quality of life.

showed that at 3 and 6 mo, there were no significant differences between the groups in the severity of incontinence, prevalence of bacteriuria, or results of vaginal cultures [70].

An impressive study has been published by Hendrix et al. [71] on 27 347 healthy postmenopausal women with the aim to assess the effects of menopausal hormone therapy on the incidence and severity of symptoms of stress, urge, and mixed UI. Women were randomized based on hysterectomy status to active treatment or placebo in either the estrogen plus progestin or the estrogen-alone trials. The combination hormones were 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate; estrogen alone consisted of 0.625 mg/d of conjugated equine estrogen. The authors reported that hormone therapy increased the incidence of all types of UI at 1 yr among women who were continent at baseline. The risk was highest for stress UI (combination relative risk [RR], 1.87; estrogen-alone RR, 2.15), followed by mixed UI (combination RR, 1.49; estrogen-alone RR, 1.79). The combination treatment had no significant effect on developing UUI (RR, 1.15), but estrogen alone increased the risk (RR, 1.32). Among women experiencing UI at baseline, frequency worsened in both groups. Amount of UI worsened at 1 yr in both trials. Women receiving menopausal hormone therapy were more likely to report that UI limited their daily activities and bothered or disturbed them at 1 yr. These results led to the statement that estrogen alone or in combination with a progestin increased the risk of UI among continent women and worsened the characteristics of UI among symptomatic women after 1 yr [71].

3.2.6.1. Comment. This last RCT offers surprisingly strong evidence against the use of systemic estrogens in the prevention or treatment of UI increasing the risk of developing de novo UUI in women continent at baseline and worsening symptoms in UUI women at baseline [71]. Other trials were limited by a very small sample size, underpowered outcomes, and short periods of treatment and follow-up (Table 16).

3.2.7. Combination of estrogens and phenylpropanolamine

Phenylpropanolamine (PPA) is an indirect sympathomimetic agent that acts by inducing norepinephrine release and thereby activating adrenergic receptors [72]. Although in most of the western countries PPA is no longer available due to a purported increased risk of stroke in younger women, our literature search led to two RCTs on its combination with estrogens.

In 1988, Kinn and Lindskog [73] enrolled 36 postmenopausal women with SUI. After an initial 4-wk single-blind period with PPA 50 mg/b.i.d., either estriol 2 mg/d or estriol and PPA were given randomly in 4-wk periods, in a crossover design. UI episodes were significantly reduced by both estriol and PPA given separately as single treatment (28%) or when given as combined therapy (40%) [73]. Aligned conclusions were described by Ahlström et al. [74]s in 1990. Twenty-nine postmenopausal women with SUI were treated with estriol 4 mg/d and randomized

Table 15 – Women: antimuscarinic and estrogen combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Tseng et al (2009) [68]	1b	2005	80	2 mg tolterodine b.i.d./ vaginal conjugated equine estrogen 0.625 mg twice a week	12 wk	MVV (ml) at baseline and EOT UDI-6 score IIQ-7 score	65.2 (58–73)	Postmenopausal women with OAB
Serati et al (2009) [67]	1b	2004–2007	229	Tolterodine ER 4 mg/ estriol cream application once daily	12 wk	A three-point symptom-assessment scale (0 = same, 1 = improved, 2 = cured)	61 (40–85)	>40 yr old and reported absence of menses for at least 12 mo, with symptoms of OAB and urodynamically proven pure DO

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Tseng et al (2009) [68]	2 mg tolterodine b.i.d. MVV: +26.0 ml UDI-6:–2.3 IIQ-7:–3.7	NA	NA	NA	NA	NA	2 mg tolterodine b.i.d./ vaginal estrogen 0.625 mg twice a week MVV: +26.1 ml UDI-6:–1.7 IIQ-7:–3.3 Significant vs tolterodine alone	–	–	–	–	–
Serati et al (2009) [67]	Tolterodine ER 4 mg 2: 62% 1: 17.8% 0: 19.4%	NA	NA	NA	NA	NA	Tolterodine ER 4 mg/ estriol cream 2: 62% 1: 20% 0: 18% Not significant vs tolterodine alone	–	–	–	–	–

DO = detrusor overactivity; EOT = end of treatment; ER = extended release; IIQ = Incontinence Impact Questionnaire; LoE = level of evidence; MVV = mean voided volume; NA = not available; OAB = overactive bladder; UDI = Urogenital Distress Inventory.

Table 16 – Women: estrogen and progestin combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Kok et al (1999) [69]	1b	1997	95	2 mg 17 beta-estradiol in combination with 2.5, 5, 10 or 15 mg dydrogesterone, orally once a day	24 wk	Urinary incontinence, frequency, and nocturia	52 ± 3.8	Amenorrheic for at least 12 mo, confirmed by serum FSH (>35 IU/l), LH (>10 IU/l), and estradiol (<120 pmol/l)
Ouslander et al (2001) [70]	1b	NR	32	Oral estrogen (0.625 mg) + progesterone (2.5 mg) or placebo, daily for 6 mo	24 wk	Change from baseline to EOT in MVV	88	Postmenopausal women with UI
Hendrix et al (2005) [71]	1b	1993–1998	27 347	(1) 0.625 mg/d of conjugated equine estrogen (CEE) + 2.5 mg/d of medroxyprogesterone acetate (MPA) vs placebo (2) 0.625 mg/dl CEE vs placebo	52 wk (1 yr)	Incident UI at 1 yr among women without UI at baseline and severity of UI at 1 yr among women who had UI at baseline	50–79 yr	Postmenopausal women with with/without UI randomized based on hysterectomy status to active treatment or placebo in either estrogen plus progestin or estrogen-alone trials

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kok et al (1999) [69]	NA	NA	NA	NA	NA	NA	2 mg 17 beta-estradiol/ 2.5 mg dydrogesterone, orally once a day Significant decrease of frequency and nocturia regardless progesterone dose	2 mg 17 beta-estradiol/ 5 mg dydrogesterone, orally once a day Significant decrease of frequency and nocturia regardless progesterone dose	2 mg 17 beta-estradiol/ 10 mg dydrogesterone, orally once a day Significant decrease of frequency and nocturia regardless progesterone dose	2 mg 17 beta-estradiol/ 15 mg dydrogesterone, orally once a day Significant decrease of frequency and nocturia regardless progesterone dose	–	–
Ouslander et al (2001) [70]	NA	NA	NA	NA	NA	MVV: + 10 ml	Oral estrogen (0.625 mg) + progesterone (2.5 mg) MVV:–10 ml **Not** significant vs placebo	–	–	–	–	–
Hendrix et al (2005) [71]	0.625 mg/dl CEE(1) Continent baseline**:** SUI RR, 2.15 (95% CI, 1.77–2.62), MUI RR, 1.79 (95% CI, 1.26–2.53), UUI RR, 1.32 (95% CI, 1.10–1.58) (2) UI at baseline: frequency RR, 1.47 (95% CI, 1.35–1.61)	NA	NA	NA	NA	NR	0.625 mg/d of CEE + 2.5 mg/d of MPA (1) Continent baseline: SUI RR, 1.87 (95% CI, 1.61–2.18), MUI RR, 1.49 (95% CI, 1.10–2.01). Not significant on UUI (2) UI at baseline: frequency RR, 1.38 (95% CI, 1.28–1.49)	–	–	–	–	–

CI = confidence interval; EOT = end of treatment; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LoE = level of evidence; MUI = mixed urinary incontinence; MVV = mean voided volume; NA = not available; NR = not reported; RR = relative risk; SUI = stress urinary incontinence; UI = urinary incontinence; UUI = urge urinary incontinence.

Table 17 – Women: estrogen and phenylpropanolamine combination trial characteristics and outcome measures

Trial	LoE	Years trial was performed	Patient number (female/total)	Drug (dose)	Trial duration	Primary endpoint	Age of patients	Inclusion criteria
Kinn and Lindskog (1988) [73]	1b	NR	36	Estriol (2 mg/d) and PPA (50 mg/b.i.d.) alone and in combination	8 wk	Micturitions/24 h (M24), leakage episodes/24 h (LE24), leakage amount/24 h (LA24), MUCP	66 (49–82)	Postmenopausal women with SUI confirmed either on coughing in a standing position during urodynamic examination or during a standardized physical strain program with filled bladder
Ahlström et al (1990) [74]	1b	NR	29	Estriol 4 mg/d and either PPA 50 mg/b.i.d. or placebo	12 wk	M24, LE24, LA24, MUCP	63 (51–73)	Postmenopausal women with symptoms of SUI verified by observation of leakage at coughing and by urodynamics

Trial	Change of symptom score from baseline											
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Placebo	Combination 1	Combination 2	Combination 3	Combination 4	Combination 5	Combination 6
Kinn and Lindskog (1988) [73]	Estriol (2 mg/d)	PPA (50 mg/b.i.d.)	NA	NA	NA	NA	Estriol (2 mg × 1) and phenylpropanolamine (50 mg × 2) M24:–0.8, LE24:–1.8. LA24:–2.8, MUCP standing: + 5.3 Significant vs estriol alone vs phenylpropanolamine alone	–	–	–	–	–
Ahlström et al (1990) [74]	Estriol (4 mg/d)	PPA (50 mg/b.i.d.)	NA	NA	NA	NA	Estriol (4 mg/d) + PPA (50 mg/b.i.d.) M24: NS, LE24:–28%, and MUCP standing: +5 Significant vs estriol alone	–	–	–	–	–

LoE = level of evidence; MUCP = maximal urethral closure pressure; NA = not available; NR = not reported; NS =not significant; PPA = phenylpropanolamine; SUI = stress urinary incontinence.

to either PPA 50 mg/b.i.d. or placebo for a period of 6 wk. During urodynamic recordings, the maximum urethral closure pressure increased by 22% with combined treatment ($p < 0.001$) and an additional effect of PPA to estriol was shown ($p = 0.022$). The number of UI episodes was reduced by 28% with combined treatment ($p = 0.007$), but not with estriol alone ($p = 0.08$) [74].

3.2.7.1. Comment. Both the trials are underpowered for efficacy and safety outcomes given the small number of patients. Therefore, these old papers have been reported herein for historical completeness (Table 17).

4. Conclusions

The most studied combination therapy for the treatment of male LUTS is the α1-blocker/5-ARI combination. This combination appears to be more efficacious in terms of several outcome variables, in particular in men who have moderate-to-severe LUTS and are at risk of disease progression (higher PV, higher PSA concentration, advanced age, higher PVR, lower Qmax, etc.). Also in terms of nocturia improvements, this combination is significantly more effective than the monotherapy. The other highly studied combination treatment both in male and in female patients with LUTS was the combination of antimuscarinics (in particular solifenacin) and mirabegron. This combination is more effective in comparison with monotherapies in terms of UI and urgency UI episodes and other parameters, without any increase of adverse events. The introduction of hormone therapy to antimuscarinics does not seem to be useful in women with LUTS.

This systematic review contains the most updated data about combination treatments for LUTS in men and women, with the aim to report the current state of the art on the different combination approaches to non-neurogenic LUTS. In common clinical practice, patients are often treated by nonstandardized combinations of pharmacological treatments. Comorbidities are often present, and sometimes this aspect could condition the treatment strategy. However, it should always be considered that the available guidelines and recommendations are intended to treat the index patients but could not always be adequate for the complicated ones. Thus, a tailored approach intended to optimize the benefit/risk ratio should be used in several cases. The holy grail of the combination therapies should be to reduce the dose of an individual agent that may able to have a synergistic effect with other agents, thus minimizing side effects and optimizing efficacy. Combination of therapies may lead to enhanced efficacy or equal efficacy with reduced adverse effects. However, compliance may be affected, additional components may be futile, and cost may be increased. Although BPE medical management seems to be more cost saving than TURP for different specific treatment durations and strategies (monotherapies vs combinations), cost depends on both medication class and individual country assessed [75]. Cost analysis studies are mandatory to better clarify the role of different treatment approaches in both women and men.

In the light of these considerations, further and fully powered studies are needed to justify the use of combined therapies for treating non-neurogenic LUTS.

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Appendix A. Supplementary data

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