Draft Comparative Effectiveness Review

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Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and adverse effects of drugs newly used within several drug classes (i.e., alpha blockers – silodosin; anticholinergics - tolterodine, solifenacin, fesoterodine; beta-3 adrenoceptor agonists – oxybutynin; phosphodiesterase type 5 (PDE-5) inhibitors - tadalafil, sildenafil) to treat lower urinary tract symptoms attributed to BPH.

Data sources. Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and Ovid Embase bibliographic databases; hand searches of references of relevant studies.

Review methods. We searched bibliographic databases from earliest electronic indexing through March 2015. Two investigators screened titles and abstracts of search results and full-text of relevant references for eligibility. Eligible studies included randomized controlled trials (RCTs) and long-term (≥1 year duration) observational studies for long-term adverse effects. We assessed risk of bias for RCTs, extracted data, pooled data for analysis when appropriate and feasible and evaluated strength of evidence for comparisons and outcomes.

Results. We searched bibliographic databases through January 2015 for studies testing specific drugs or combinations that included newly used drugs. We synthesized evidence from 55 unique trials and 7 observational studies. All trials lasted less than 3 months. Silodosin was more effective than placebo in improving LUTS, but was similar to tamsulosin, and there were more adverse effects with silodosin. Patients often discontinued silodosin during long term treatment. Solifenacin/alpha blocker (AB) combination therapy was better than placebo, but tolterodine/AB combination therapy and solifenacin/AB combination were similar to AB monotherapy, and there were more adverse effects with combination therapy. Tadalafil improved LUTS more than placebo but had more adverse effects. Tadalafil/AB combination improved LUTS more than AB monotherapy. Tadalafil and tamsulosin had similar efficacy and adverse effects. During long-term treatment with tadalafil, adverse effects were frequent. All effect sizes were small. There was insufficient evidence to assess efficacy or adverse effects of mirabegron. Evidence was insufficient on long-term effectiveness including prevention of symptom progression, acute urinary retention or need for surgical intervention.

Conclusions. Several drugs newly used, along or in combination with traditional drugs, to treat LUTS attributed to BPH show some evidence of short-term symptom efficacy. However, the effect size is small, adverse effects are higher, and newer drugs are not superior to traditional alpha-blocker therapy. Data were not available to assess long-term maintenance, prevention of disease progression (including acute urinary retention or need for surgical intervention), and adverse effects.

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Introduction

Benign Prostatic Hyperplasia (BPH) is a "histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone."[1] Half of men over the age of 40 develop BPH.[2]

About half of men with BPH develop an enlarged prostate gland, called benign prostatic enlargement (BPE); among these, about half develop bladder outlet obstruction (BOO).[3] BOO and/or changes in smooth muscle tone and resistance that can accompany BPH often result in lower urinary tract symptoms (LUTS).[1] LUTS include storage disturbances (such as daytime urinary urgency and nocturia) and/or voiding disturbances (such as urinary hesitancy, weak stream, straining, and prolonged voiding).[2] LUTS affect an estimated 3 percent of men ages 45–49 years old increasing to around 30 percent of men over 85 years old.[2] Urinary hesitancy, weak stream, and nocturia are the most commonly reported LUTS.[4] BPH/LUTS negatively impact quality of life[2,3] and cost the United States over $1 billion annually.[3]

Usually, BPH diagnosis is based on clinical presentation of bothersome LUTS or enlarged prostate on digital rectal exam, though when LUTS is present, causes other than BPH still should be ruled out.[3] Consensus recommendations from the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases presented guidance for evaluation of older men with LUTS atttributed to BPH (LUTS/BPH).[5] In patients with LUTS/BPH, treatment decisions can typically be based on symptoms without need to perform uroflowmetry and postvoid residual urine (PVR) measurement.[3] However, recent evidence suggests that BPH that has progressed to BOO may not be accurately diagnosed with the basic evaluation. If findings from the basic evaluation do not suggest complicated LUTS, which may require urologist referral, then treatment should be based on the degree of bother.[5]

Medical management is typically the first-line treatment. Goals of medical management are to reduce symptoms and prevent or delay disease progression. Trends in medical management of LUTS/BPH have progressed over the last 25 years. Table 1 provides a list of drugs commonly used to treat LUTS/BPH. Alpha blockers (ABs) and 5-alpha reductase inhibitors (5-ARIs) have been used to treat LUTS/BPH for decades and their efficacy has been established. Recently, newer drugs and other drug classes have shown promise in treating LUTS/BPH (Table 1). A new AB, silodosin, was approved for BPH in 2008.[6] Several anticholinergics drugs approved for overactive bladder (OAB) symptoms, including urinary urgency, frequency and nocturia, have the potential to alleviate similar symptoms of LUTS/BPH.[7] These anticholinergic drugs work directly on the bladder smooth muscle as opposed to ABss and 5-ARIs, which work directly on the prostate. Anticholinergics have been used more frequently for LUTS/BPH since the TIMES trial reported in 2006 that significantly more men with overactive bladder plus LUTS had treatment benefit from combined tolterodine ER plus tamsulosin than from either monotherapy or placebo.[8]

A new class of drugs, beta-3 adrenoceptor agonists, was recently developed to treat OAB. Their proposed advantages over anticholinergics include potentially lower rates of adverse effects and potentially smaller risk of urinary retention.[7] Preliminary evidence suggests that these drugs may effectively treat LUTS/BPH, and their use for LUTS/BPH may increase in the future.[9]

Tadalafil, a phosphodiesterase type 5 inhibitor (PDE-5), was FDA-approved for the treatment of erectile dysfunction (ED) in 2003 and for the treatment of BPH in 2011. The common pathology and the high rate of comorbidity between LUTS/BPH and ED likely influenced the early use of ED drugs for LUTS/BPH.[10,11] PDE-5 inhibitors have been used off-label for LUTS/BPH, both alone and in combination with ABs.

Based on the wide variety of medications available to treat LUTS/BPH, it is possible that tailoring treatment with single medications or medication combinations can maximize efficacy and minimize adverse effects. Some patients are more bothered by specific symptoms that may be preferentially improved by certain medications. Men with LUTS/BPH often have other health concerns common in older men and may be on other medications. These factors should be considered in medical management of LUTS/BPH.

The primary goals of LUTS/BPH treatment are to reduce LUTS, improve prostate-related quality of life, and prevent or delay disease progression. The two most widely used, validated instruments for assessment of LUTS are the American Urological Association Symptom Index (AUA-SI) and the International Prostate Symptom Score (I-PSS).[6]

Intermediate outcomes such as specific urodynamic parameters (i.e., peak flow, detrusor pressure) are often reported in research. However, these outcomes are not patient centered, and it is unclear whether they should guide treatment decisions.

Current clinical practice guidelines are relevant to current practice. However, these guidelines need to be updated to account for more recently approved medications for LUTS/BPH. Our review comprehensively assesses medications for LUTS/BPH that have been newly used in the last 10 years. In this report, we synthesized available data regarding efficacy, comparative effectiveness, and adverse effects of one new AB (silodosin); all anticholinergics, beta-3 agonists, and PDE-5 inhibitors; and medication combinations that include these agents. The addition of this evidence synthesis to what already is understood about the earlier developed ABs, 5-ARIs, and AB/5-ARI combinations will provide a comprehensive assessment of all medical management options for LUTS/BPH.

We address the following Key Questions as they pertain to the PICOTS (population, interventions, comparisons, outcomes, timing, and setting) described in Table 2:

Key Questions

Key Question 1: What is the efficacy and comparative effectiveness of newer medications alone or in combination for LUTS attributed to BPH?

Key Question 2: What are the harms and comparative harms of newer medications for LUTS attributed to BPH?

Key Question 3: Do the comparative benefits and harms of newer medications for LUTS attributed to BPH differ according to demographic or clinical characteristics?

Table 1. Medications used to treat LUTS attributed to BPH

Drug Class - Mechanism of action [FDA]	**Newer Medication** Older Medication
Alpha 1 blockers (ABs): inhibit prostate and bladder neck smooth muscle contraction by blocking their alpha-1 receptors, thus decreasing resistance to urinary flow; Since the bladder body only has a negligible density of alpha-1 receptors, alpha-1-blockers reduce bladder outlet resistance without impairing bladder emptying. Alpha-1 blockers also may regulate prostate growth by inducing apoptosis in both the epithelial and stromal smooth muscle cells without affecting the rate of cell proliferation.	**Silodosin[a] [Rapaflo]** Terazosin[a] [Hytrin]; Alfuzosin[a] [Uroxatral]; Doxazosin[a] [Cardura]; Tamsulosin[a] [Flomax]
5 alpha reductase inhibitors (5-ARIs): inhibit 5alpha-reductase, an isoenzyme that metabolizes testosterone to dihydrotestosterone (DHT) in the prostate gland, liver, and skin; blocking conversion of testosterone to DHT and reducing serum and tissue DHT.	Finasteride[a] [Proscar] Dutasteride[a] [Avodart]
Anticholinergic agent: relaxes bladder smooth muscle by reducing the muscarinic effect of acetylcholine on smooth muscle.	**Oxybutynin[b] [Oxytrol]; Fesoterodine[b] [Toviaz]; Darifenacin[b] [Enablex]; Tolterodine[b] [Detrol, Detrol LA]; Solifenacin[b] [Vesicare]; Trospium[b] [Sanctura]**
Beta-3 adrenergic agonist: Increases bladder capacity by relaxing the bladder smooth muscle during the storage phase of the urinary bladder fill-void cycle	**Mirabegron[b] [Myrbetriq]**
Phospodiesterase type 5 (PDE-5) inhibitors: selectively inhibits PDE5 and increases cyclic guanosine monophosphate (cGMP). The smooth muscle cells of the prostate, bladder and surrounding vasculature contain PDE5; inhibiting PDE5 and increasing cGMP levels in these tissues causes smooth muscle relaxation.	**Tadalafil[a, d] [Cialis]; Sildenafil[c] [Viagra]; Avanafil[d] [Stendra]; Vardenafil[d] [Staxyn, Levitra]**

[a] FDA approved to treat BPH; [b] FDA approved to treat overactive bladder; [c] FDA approved to treat erectile dysfunction and pulmonary artery hypertension; [d] FDA approved to treat erectile dysfunction.
Bolded medications are the medications that are the focus of this review.
cGMP=cyclic guanosine monophosphate; DHT= dihydrotestosterone

Table 2. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

PICOTS Element	**Description**
Population(s)	Adult men (age 45 years and over) with LUTS attributed to BPH, overall and in subgroups defined by BMI, erectile dysfunction, LUTS severity, and previous LUTS treatment.
Interventions	Newer LUTS/BPH medications: ABs (silodosin); Anticholinergics (oxybutynin, fesoterodine, darifenacin, tolterodine, solifenacin, trospium); Beta-3 adrenoceptor agonists (mirabegron); PDE-5s (tadalafil, sildenafil, avanafil, vardenafil); Adjunctive/combination treatment with newer medication
Comparators	Placebo or “older” LUTS/BPH medication (i.e. previously FDA approved for BPH) (Table 1)
Outcomes	Primary Outcomes: LUTS scores (I-PSS, AUA-SI scores); Prostate-related bother or quality of life (QoL) (I-PSS QoL question, BPH/LUTS impact (BII) scale); Disease Progression/Treatment Failure (prevention/delay of need for surgical intervention, acute urinary retention (AUR), 3-point increase in I-PSS score). Adverse effects: Common and serious medication side effects
Timing	Short term: treatment duration of 1 to less than 6 months Intermediate: treatment duration of at least 6 months and less than 1 year Long term: treatment duration of 1 year or more
Setting	Outpatient settings

AUR=Acute urinary retention; BMI=Body mass index; BPH=Benign prostatic hyperplasia; FDA=Food and Drug Administration; LUTS=Lower urinary tract symptoms

Methods

We developed an analytical framework to guide the systematic review process (Appendix A). We looked for randomized controlled trials (RCTs) that tested the efficacy or comparative effectiveness of treatments involving newer drugs in men with LUTS attributed to BPH. We searched Ovid Medline®, Ovid Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) using subject headings and natural language for the concept of BPH and each drug with filters for study design (Appendix B) to identify relevant RCTs. We additionally searched for large (n≥100), longer-term observational studies to assess long-term or rare treatment associated harms. We supplemented the bibliographic database search with forward and backward citation searching of relevant systematic reviews and other key references. We will update searches while the draft report is under public/peer review.

Titles and abstracts were screened by two independent investigators to identify studies meeting PICOTS framework. All studies identified as relevant by either investigator underwent full-text screening. Two investigators conducted full-text screening to determine if inclusion criteria were met. Differences in screening decisions, which were uncommon, were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We searched ClinicalTrials.gov and the Food and Drug Administration Web site to identify additional completed and ongoing studies and to assess publication bias.

Data were extracted to evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator. Data were extracted from crossover trials at time points before crossover. Post-crossover data were not used. Risk of bias of eligible studies was assessed using AHRQ guidance by one investigator and reviewed by a second.[12] Relevant components included participant selection, method of randomization, attrition, blinding, allocation concealment, and appropriateness of analytic methods. We consulted to reconcile discrepancies in overall risk of bias assessments. Overall summary risk of bias assessments for each study were classified as low, moderate, or high based upon the collective risk of bias and confidence that the study results are believable given the study's limitations. If trials with high risk of bias had results different than higher quality trials, we explored sensitivity analysis.

We assessed clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[13] Data were pooled using a DerSimonian-Laird random effects model in RevMan.[14] We calculated risk ratios (RR), absolute risk differences (ARD), and number needed to treat or harm (NNT, NNH) with corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes. We assessed statistical heterogeneity with Cochran's Q test and measured the magnitude of heterogeneity with the I^2 statistic.[13] If substantial heterogeneity was present (i.e. $I^2 \geq 70\%$), we stratified the results to assess treatment effects based on patient or study characteristics and/or explored sensitivity analyses. When there were statistically significant differences in specific LUTS/BPH outcomes between treatment groups, we interpreted efficacy and comparative effectiveness using established thresholds for these measures when they were available. Table 3 provides a list of these instruments, basic characteristics, and relevant thresholds for classifying improvement.[15] Barry et al. conducted an anchor-based study to identify the minimal detectable difference (MDD) in I-PSS and BII scales. For outcomes measured with instruments that lack established thresholds, we calculated standard effect sizes and required a small effect size or larger to conclude efficacy or comparative effectiveness.

Unfortunately, few trials conducted responder analyses. Most reported only mean scale scores or mean change in scale scores for instruments with established MDDs. Further, no studies have identified minimally important differences (MID) relevant to interpreting differences between groups. Therefore, to qualitatively estimate the proportion of patients who may have benefitted from one treatment versus placebo or control, we examined how the between-group WMD compared to the MDD for each outcome of interest. WMDs between groups equal to or larger than MDD suggested that many patients may have gained detectable benefits from treatment; WMDs between one-half of the MDD and the MDD suggest that the treatment may be detected by an appreciable number of participants; and WMDs below one-half of the MDD suggest that it is unlikely that an appreciable number of participants achieve detectable benefits.[18]

The overall strength of evidence (SoE) for primary outcomes of KQ1 within each comparison was evaluated based on five required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size among studies); (4) precision (degree of certainty around an estimate assessed in relationship to MDD); and (5) reporting bias.[19] Based on these elements, we assessed the overall SoE for each comparison and outcome as:[19]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Applicability of studies was determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population (age, race, and country from which the study participants were enrolled), narrow eligibility criteria, and patient and intervention characteristics potentially associated with treatment response different than those described by population studies.[20]

Table 3: Symptom and quality of life scales measuring LUTS attributed to BPH

Instrument	Range (Points)	Scoring	Thresholds Relevant to Assessing Effectiveness*[15]
International Prostate Symptom Score (I-PSS)[a]	0 (asymptomatic) to 35 (very symptomatic)	0 to 7: Mild symptoms 8 to 19: Moderate symptoms 20 to 35: Severe symptoms	-3=slight improvement -5.1=moderate improvement -8.8=marked improvement
BPH Impact Index (BII)	0 to 13	Higher scores represent increased perceived impact of BPH-LUTS on overall health	-0.5=slight improvement -1.1=moderate improvement -2.2=marked improvement
I-PSS QoL due to Urinary Symptoms	0 to 6	0-2: Delighted to mostly satisfied 3: Mixed 4-6: Mostly dissatisfied to terrible	No thresholds identified in the literature; we used a MDD of -1 because this is an ordinal scale and a reduction from a higher (worse) level to a lower one represents a qualitative improvement.

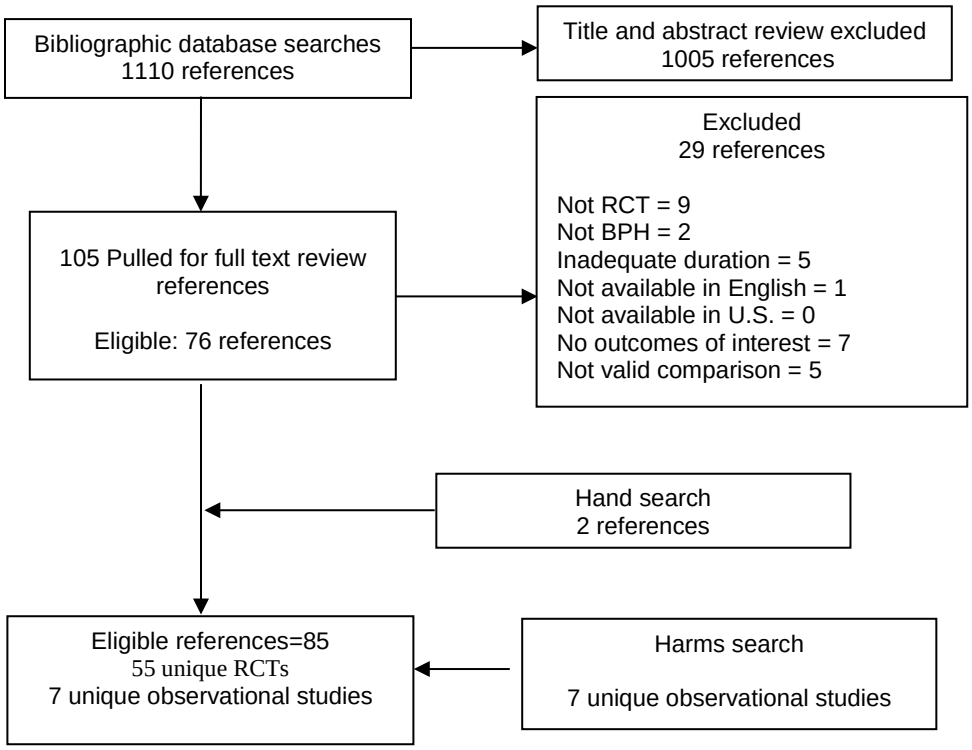
[a] Also known as the American Urological Association symptom score
BPH-LUTS=benign prostatic hyperplasia-lower urinary tract symptoms; QoL=Quality of life
* Based on a baseline AUA-SS of approximately 16.

Results

Search Results

Our search identified 1110 citations, of which 105 required full text review after title and abstract screening and 76 met eligibility criteria for inclusion in this review (Figure 1). Hand searching identified another two eligible articles, for a total of 78 articles reporting 55 unique RCTs. Of the articles we identified and determined to be eligible, silodosin was studied in 10 trials (reported in 17 articles);[21-37] anticholinergics were studied in 19 trials[38-56] (reported in 24 articles);[38-61] beta-3 agonists were studied in 2 trials (reported in 2 articles);[62,63] and PDE-5 inhibitors were studied in 24 trials[64-87] (reported in 35 articles).[64-98] Our search for studies reporting long-term adverse effects, to supplement harms reported in RCTs, identified seven eligible observational studies.[71,99-104]

Figure 1. Literature flow diagram



The results are presented separately for each of four drug classes (new ABs, anticholinergics, beta-3 agonists, and PDE-5s), and specific drugs are listed within each class. The outcomes addressed by the three key questions are discussed within each drug-specific section.

New Alpha Blocker

Supporting tables and figure relevant to new ABs appear in Appendix D.

Key Points

- Silodosin, the only new AB, improved LUTS more than placebo over short-term treatment (3 mos);) treatment response was greater and I-PSS scores decreased more with silodosin; effect size was small (Moderate to High SoE).
- Adverse effects with silodosin were higher than with placebo (High SoE).
- Silodosin and tamsulosin were similarly effective in improving LUTS over short-term treatment (Moderate SoE), though adverse effects were more frequent with silodosin (Moderate SoE).

Efficacy of Silodosin

Three reports of four eligible trials randomized males with BPH (n=1759) to silodosin 8 mg daily (as 8 mg once a day or 4 mg twice a day) versus placebo, with all trials lasting 3 months (Table 4).[27,29,30] Mean age of participants was 63 years and mean baseline I-PSS score was 20 (range 17.1 to 21.3). In the two trials that reported race/ethnicity, nearly all participants were white (93 percent).[27,29] Two trials were conducted in the United States,[29] one in Europe,[27] and one in Japan.[30] Three trials reported industry sponsorship[27,29] and one did not report sponsorship.[30] Overall risk of bias was low in 3 trials[27,29] and was moderate in 1 trial.[30]

Two trials conducted a responder analysis, defined as ≥25 percent reduction in baseline I-PSS score. The proportion of responders was higher with silodosin than placebo (70 percent vs. 51 percent, RR 1.38 [95% CI, 1.21 to 1.57]), a 19 percent increase in absolute risk of response (High SoE). Mean change in I-PSS scores also was larger with silodosin than placebo (WMD = -2.7; 95% CI: -3.2 to -2.1). Men randomized to silodosin 8 mg daily experienced a mean reduction in I-PSS scores of 6.9 points compared with a mean reduction of 4.0 points for those assigned to placebo. Silodosin improved LUTS attributed to BPH more than placebo (moderate SoE). Two trials reported the I-PSS QoL index as a categorical outcome.[27,33] Improvement in the I-PSS QoL favored silodosin, with 37 percent reporting being "delighted, pleased, or mostly satisfied" compared with 26 percent with placebo (high SoE). One trial assessed I-PSS QoL with improvement based on mean change from baseline of -1.7 and -1.1 points for the silodosin and placebo groups, respectively (WMD = -0.60; 95% CI: -0.92 to -0.28). None of the trials reported disease progression or treatment failure outcomes.

Study withdrawal for any reason was similar with silodosin or placebo (low SoE).[27,29] Withdrawal due to adverse effects was higher with silodosin than placebo (high SoE). More participants reported one or more adverse effects with silodosin than placebo (53 vs. 38 percent; RR 1.38; 95% CI: 1.19 to 1.60) (high SoE). The most common adverse effect with silodosin was abnormal ejaculation, 22 percent with silodosin and less than 1 percent with placebo (RR 25.06; 95% CI: 11.55 to 54.37). Serious adverse effects were infrequent and similar with silodosin or placebo, approximately one and two percent respectively.[29] Chapple et al. reported serious adverse effects (including prostate cancer and death) in approximately one percent of participants overall, but did not report this outcome separately by treatment group.[27]

Table 4. Evidence overview: silodosin versus placebo

Silodosin 8 mg vs. Placebo ***(4 RCT[27,29,30]; N=1759)***	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Placebo Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
Responders based on total I-PSS score	2 (819)	70 (381/545)	51 (139/274)	Favors silodosin RR = 1.38 [1.21 to 1.57] ARD = 0.20 [0.11 to 0.29] NNT = 5	High
I-PSS score, *mean change from baseline*	4 (1743)	-6.9	-4	Favors silodosin WMD = -2.68 [-3.24 to -2.11]	Moderate (imprecise)
I-PSS QoL, reporting "delighted, pleased, or mostly satisfied'	3 (1494)	37 (312/847)	26 (166/647)	Favors silodosin RR = 1.36 [1.61 to 1.59] ARD = 0.09 [0.05 to 0.14] NNT = 12	High
I-PSS QoL, *mean change from baseline*	1 (264)	-1.7	-1.1	Favors silodosin MD = -0.60 [-0.92 to -0.28]	Moderate (imprecise)
Withdrawals due to adverse effects	3 (1759)	5 (56/1023)	2 (17/736)	Greater with silodosin RR = 2.41 [1.41 to 4.12] ARD = 0.03 [-0.00 to 0.06]	High
Participants with ≥1 adverse effect	4 (1757)	53 (545/1022)	38 (277/735)	Greater with silodosin RR = 1.38 [1.19 to 1.60] ARD = 0.16 [0.11 to 0.20] NNH = 7	High

ARD=absolute risk difference;; CI=confidence intervals; I-PSS=International Prostate Symptom Score;; NNH=number needed to harm; NNT=number needed to treat; QoL=quality of life; RR=risk ratio; MD=mean difference; WMD=weighted mean difference

Long-term Adverse Effects

We identified four observational studies reporting longer-term adverse effects related to silodosin treatment.[100-102,104] Kim et al. analyzed medical records of males on four ABs (doxazosin, tamsulosin, alfuzosin, and silodosin) for LUTS/BPH from 2008 through 2012 to examine reasons for prescription change (n=3200).[100] After a mean of nearly 11-weeks, 21 percent changed ABs, including 26 percent for both doxazosin and alfuzosin, 20 percent with tamsulosin, and 16 percent with silodosin (p<.05 for silodosin compared to other groups).. Patients most commonly changed ABs for lack of efficacy (53 percent), adverse effects (33 percent), relative cost (7 percent), "inconvenience of taking drugs" (4 percent), and cardiovascular comorbidity (3 percent). Patients changed prescriptions because of cost more often with tamsulosin (13 percent) than the other three ABs (1 to 2 percent); and more often due to cardiovascular comorbidities with doxazosin (9 percent) than tamsulosin (2 percent) or silodosin (0 percent). Specific adverse effects causing prescription change were more likely hypotension-related with doxazosin (40 percent) than tamsulosin (13 percent) or silodosin (3 percent); and more likely ejaculation disorder or failure with silodosin (74 percent) compared with the other three ABs (5 to 11 percent).

Sakata et al. interviewed patients who had been taking silodosin for LUTS/BPH for a mean of 6.7 months at one hospital to evaluate the extent and impact of associated ejaculatory dysfunction. associated with the drug.[102] Of the 91 patients prescribed silodosin, 42 percent experienced ejaculatory disorder.However, when only those reporting sexual activity were considered, 95 percent experienced ejaculatory disorder. Seventy-six percent of those patients were bothered by the adverse effect. nevertheless, the discontinuation rate because of ejaculatory disorder in patients on silodosin was only 2 percent.

Marks et al. analyzed adverse effects in a 40-week open label extension of a previous RCT.[104] Of the 661 participants who enrolled in the extension, 435 completed the extension, with

all patients taking silodosin 8 mg once a day. Thirty-four percent discontinued treatment due to adverse effects. A total of 431 experienced 924 adverse effects. Twenty-nine patients (4.4 percent) experienced serious adverse effects including two deaths; none of the serious adverse effects, including the deaths, were considered drug-related by the researchers. Criteria for determining whether serious adverse effects were drug-related were not described in the report The most common adverse effects were retrograde ejaculation (21 percent), diarrhea (4 percent), and nasopharyngitis (4 percent).

Yoshimura et al. reviewed FDA data for adverse effects associated with ABs and found the data on silodosin insufficient to compare with other ABs.[101]

Patient Demographic and Clinical Characteristics

We identified two secondary analyses that evaluated the effect of our prespecified patient demographic or clinical characteristics on the efficacy of silodosin. Novara et al. pooled data (n=1484) from two previous RCTs[27,29] to examine the effect of age, BMI, and baseline LUTS severity on response to treatment using linear regression models.[31] Treatment was the only predictive variable after adjusting for age, BMI, and baseline LUTS severity. Kawabe et al. stratified participants according to baseline LUTS severity and found that both levels of severity achieve improvements in LUTS over placebo.[30]

Dosing of Silodosin

Choo et al. compared silodosin 4 mg taken twice daily with 8 mg taken once daily for 12-weeks (n=532).[22] They found no differences in any outcome or adverse effect.

Comparative Effectiveness of Silodosin Versus Tamsulosin

Eight trials randomized males with BPH (n=1705) to silodosin 8 mg daily versus tamsulosin 0.2 to 0.4 mg daily. All trials lasted 1 to 3 months (Table 5).[21,23-28,30] Excluding the placebo arms in two of the trials, mean age of the participants was 67 years and mean I-PSS score at baseline was 18 (range 17 to 20). Six trials conducted in Asia used a 0.2 mg dose of tamsulosin,[21,23-26,30] while two trials conducted in Europe or India used a 0.4 mg dose of tamsulosin.[21,27] Only the European trial reported race/ethnicity, and all its participants were white.[27] Three trials were crossover studies (4 week phases each) and only data from the first-phases of these trials were used in the analyses.[23,26,28] Two trials reported industry sponsorship.[24,27] Overall risk of bias was low in 2 trials,[21,27] moderate in 4 trials,[23-25,30] and high in 2 trials.[26,28]

Three trials conducted responder analysis (defined as >25 percent reduction in I-PSS score).[25 2012,27,30] Response to treatment was similar with silodosin and tamsulosin. Given a mean baseline I-PSS score for these studies of 19 points, this equated to about a 5-point reduction from baseline, exceeding established MDD for individuals with mean IPSS scores similar to enrollees. Silodosin and tamsulosin were similar in improving mean I-PSS scores (WMD = -0.6; 95% CI: -1.5 to 0.2) (moderate SoE). Mean reductions in I-PSS scores were 7.8 and 7.2 points with silodosin and tamsulosin. Both treatments reduced mean I-PSS scores by more than the MDD. Overall improvement in the I-PSS QoL also was similar with silodosin and tamsulosin, but heterogeneity between studies was substantial (I^2 = 76%) (low SoE). No indicators of disease progression/ treatment failure were reported.

Among RCTs with parallel group designs, study withdrawal for any reason was similar with silodosin and tamsulosin (low SoE). Withdrawal due to an adverse effects and reporting one or more adverse effects was higher with silodosin (moderate SoE). The most common adverse

effect, abnormal ejaculation, was reported by 16 percent with silodosin versus 2 percent with tamsulosin (RR = 8.47; 95% CI, 4.86 to 14.77). Crossover trials reported that withdrawals due to adverse effects were only observed with silodosin[23,26] and that abnormal ejaculation was the most common.[23,26,28] Chapple et al. reported serious adverse effects including supraventricular arrhythmia, prostate cancer, and death in approximately one percent of participants overall but didn't report results by study arm.[27]

Table 5. Evidence overview: silodosin versus tamsulosin

Silodosin 8 mg vs. Tamsulosin 0.2-0.4mg ***(8 RCT[21,23-28,30]; N=1705)***	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
Responders, based on ≥25% reduction in total I-PSS score	3 (1283)	72 (456/632)	68 (440/651)	EQUIVALENT RR = 1.07 [0.99 to 1.15]	Moderate (moderate study limitations)
I-PSS score, *mean change from baseline*	7 (1538)	-7.8	-7.2	EQUIVALENTWMD = -0.64 [-1.46 to 0.18]	Moderate (moderate study limitations)
I-PSS QoL, *mean change from baseline*	5 (728)	-1.5 (1.3 with Chapple*)	-1.3 (1.2 with Chapple*)	EQUIVALENTWMD = -0.16 [-0.54 to 0.23]	Low (moderate study limitations, inconsistent)
Overall withdrawals	4 (1125)	9 (53/563)	9 (49/562)	EQUIVALENTRR = 1.05 [0.72 to 1.52]	Low (moderate study limitations)
Withdrawals due to adverse effects	3 (1222)	5 (30/601)	3 (16/621)	Greater with silodosin RR = 1.96 [1.08 to 3.55] ARD = 0.03 [-0.01 to 0.07]	Moderate (moderate study limitations)
Participants with ≥1 adverse effect	3 (1338)	52 (342/659)	46 (314/679)	EQUIVALENTRR = 1.11 [1.01 to 1.22] ARD = 0.06 [0.02 to 0.11] NNH = 17	Moderate(moderate study limitations)

ARD=absolute risk difference; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; NNH=number needed to harm; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference
* Data from Chapple et al. 2011 were not pooled.

Anticholinergics

Supporting tables and figures relevant to anticholinergics appear in Appendix E.

Key Points

- Tolterodine/AB combination therapy was similar to AB monotherapy for LUTS(SoE: Moderate). Withdrawals for adverse effects were higher with tolterodine/AB than AB monotherapy groups (moderate SOE).),
- Solifenacin/AB combination therapy was better than placebo in treating LUTS over the short-term though effect size was small (moderate SOE); adverse effects were more frequent with solifenacin/AB combination therapy than with placebo (moderate SOE).
- olifenacin/AB combination therapy and AB monotherapy were similar short-term treatment of LUTS more than (moderate SOE) Having more than one adverse effects was more common with solifenacin/AB combination therapy than with AB monotherapy (moderate SOE).

Tolterodine

Efficacy of Tolterodine

One 12-week, double-blind, trial compared tolterodine 4 mg daily (n=217) to placebo (n=222) in men with LUTS and OAB symptoms.[56] Individuals with a baseline post void residual of >200 ml were excluded. Mean age was 62 and mean baseline I-PSS score was 20. Most participants were white (81 percent). This industry-sponsored trial was conducted in the United States. Overall risk of bias was low.

Tolterodine was similar to placebo in effects on total I-PSS (WMD = -0.70: 95% CI: -1.88 to 0.48) or I-PSS QOL (low SoE for both outcomes). Urinary retention was reported in two and three participants in the tolterodine and placebo groups, respectively.

Total withdrawals and withdrawal due to adverse effects were similar with tolterodine and placebo (insufficient strength evidence). Dry mouth was reported more frequently with tolterodine than placebo (7 percent vs. 2 percent).

Efficacy of Tolterodine AB Combination

One 12-week trial compared the combination of tolterodine 4 mg and tamsulosin 0.4 mg daily (n=225) with placebo (n=222) in males with LUTS and OAB symptoms.[56] Individuals with baseline post void residual >200 ml were excluded. Mean age was 61 and mean baseline I-PSS was 20. This industry-sponsored trial was conducted in the United States. Risk of bias was low.

Mean change in I-PSS (MD = -1.80; 95% CI: -2.92 to -0.68) and I-PSS QOL were superior with combination therapy compared with placebo (low SoE).

Rates of withdrawal due to adverse effects were higher with combination therapy than placebo (low SoE).

Efficacy of Tolterodine Added to AB Monotherapy

Four trials randomized males with BPH (n=1249) to a combination of tolterodine 4 mg plus AB versus AB monotherapy (Table 6).[39,50,54,56] Mean age was 63 and mean baseline I-PSS score was 20 (range = 18.5 to 24.0). One study was a multicenter study from several countries (Europe, North America, Asia, and South Africa), and one was a multicenter study performed in the United States; the others were conducted in South Korea and Pakistan. All but one study reported industry sponsorship. Overall risk of bias for threetrials was low and one trial had high risk of bias.[39]

Only the one high risk of bias trial[39] conducted a responder analysis, defined as a 3-point improvement in I-PSS score from baseline, and found response higher with combination therapy (RR= 2.7; 95% CI: 1.6 to 4.7) (insufficient evidence). Pooled results from four studies show change in I-PSS scores weresimilar with combination and monotherapy (WMD = -0.19; 95% CI: -0.74 to 0.35) (moderate SoE). Pooled results from three studies showed mean change in I-PSS QoL was similar between combination and monotherapy (low SoE).

Pooled results from three trials show similar rates of acute urinary retention (AUR) between combination and monotherapy (insufficient evidence). No other indicators of disease progression/treatment failure were reported. Withdrawal for any reason was similar with combination and monotherapy (moderate SoE). Withdrawal due to adverse effects was higher with combination than monotherapy (moderate SoE). The proportion reporting one or more adverse effects was similar with combination and monotherapy in the one trial reporting this outcome (low SoE).[54]

Table 6. Evidence overview: tolterodine/AB combination versus AB monotherapy

Tolterodine, 4 mg Plus AB vs. AB ***(4 RCT[39,50,54,56]; N=1249)***	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
Responders	1 (70)	77.1% (27/35)	28.6% (10/35)	Favors Combination RR = 2.7 [1.55 to 4.70] ARD = 0.49 [0.28 to 0.69] NNT =3	Insufficient (high study imitations, unknown consistency)
I-PSS score, *mean change from baseline*	4 (1249)			EQUIVALENTWMD = -0.19 [-0.74 to 0.35]	Moderate (low to moderate study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	3 (1182)			EQUIVALENTWMD=-0.34 [-0.73, 0.06]	Low (imprecise, inconsistent)
Acute urinary retention	3 (1268)	1% (6/639)	0% (2/629)	EQUIVALENTOR=2.69 [0.67, 10.80]	Insufficient (indirect, very imprecise)
Overall withdrawals	3 (1268)	16% (101/639)	14% (88/629)	EQUIVALENTRR=1.11 [0.79, 1.56]	Moderate (imprecise)
Withdrawals due to adverse effects	3 (1268)	6% (36/639)	3% (16/629)	Greater with Combination RR=2.17 [1.21, 3.88] ARD = 0.03 [0.00 to 0.05] NNH = 34	High
Participants with ≥1 adverse effect	1 (652)	35% (114/329)	28% (89/323)	Greater with Combination RR=1.26 [1.00 to1.58] (p = .052)	Low (imprecise, unknown consistency)

ARD=absolute risk difference; CI=confidence intervals; I-PSS=International Prostate Symptom Score; ND=no statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Patient Demographic and Clinical Characteristics

We identified one small trial (n=70) with a high risk of bias that evaluated the adjunctive efficacy of tolterodine added to alfuzosin vs alfuzosin monotherapy by age.[39] Combination therapy improved symptoms more than monotherapy in men between 51 and 70, but not in those 50 and under or over 70.

Efficacy of Tolterodine Added to AB or 5ARI Monotherapy

One 52-week trial compared a combination of tolterodine 4 mg daily plus doxazosin 4 mg daily (AB) and/or dutasteride 0.5 mg daily (5ARI) (n=50) versus doxazosin and/or dutasteride monotherapy (n=87) in men with LUTS and storage symptoms.[52] Individuals with a baseline post void residual of >250 ml were excluded. The men were older, with a mean age of 76, and mean baseline I-PSS score was 18. Industry-sponsorship was not reported and the trial was conducted in Taiwan. Overall risk of bias was high.

Change in I-PSS scores was similar with the tolterodine plus doxazosin/dutasteride combined group and the doxazosin/dutasteride group with change scores of -8.9 versus -6.5 (P = .12), respectively. Change in I-PSS QoL scores was also similar between groups.

Acute urinary retention requiring catheterization was comparable between groups, two participants (4 percent) in the tolterodine plus doxazosin/dutasteride combined group and three (3.5 percent) in the the doxazosin/dutasteride group. Withdrawals and proportions with adverse effects were not reported by treatment arm. Dry mouth was reported more frequently with tolterodine plus doxazosin/dutasteride combined therapy (14 percent vs. 6 percent), leading to study withdrawal of six combination participants. However, SoE was insufficient for all efficacy and harms outcomes.

Comparative Effectiveness of Tolterodine Versus AB

Two trials compared tolterodine with AB monotherapy. Data were not pooled due to the heterogeneity in study populations in terms of LUTS severity.

Kaplan et al. compared tolterodine 4 mg (n=217) with tamsulosin 0.4 mg (n=222) in a 12-week double-blind trial.[56] Mean age was 62 and mean baseline I-PSS was 20. This industry-sponsored trial was conducted in the United States. Overall risk of bias was low.

Mean changes in I-PSS (MD = 0.90; 95% CI:-0.46 to 2.26) and I-PSS QOL (MD = -0.10; 95% CI: -0.21 to 0.41) were similar with tolterodine and tamsulosin groups (low SoE).

Three cases of AUR were reported with tolterodine compared to none with tamsulosin. Overall withdrawals and withdrawal due to adverse effects were similar with tolterodine and tamsulosin (insufficient evidence). Dizziness was reported more frequently with tamsulosin than tolterodine (6 percent vs. 1 percent).

Liao et al. compared tolterodine 4mg (n=108) with doxazosin 4 mg daily (n=94) in participants with predominant storage LUTS in a 12-week trial.[38] Those with baseline post void residual >250 ml were excluded. Mean age was 69 and mean baseline I-PSS was 11.5, substantially lower than the previous trial. Industry sponsorship was not reported and the trial was conducted in Taiwan. No blinding was reported and overall risk of bias was high.

Mean change in I-PSS (MD = -0.20; -2.32 to 1.92) and I-PSS QOL (MD = -0.20; -0.61 to 0.21) were similar with tolterodine and doxazosin groups (insufficient evidence). No participants developed urinary retention. No other indicators of disease progression or treatment failure were reported. Rates of total withdrawals and withdrawal due to adverse effects were similar with tolterodine and placebo. Evidence for harms outcomes was insufficient.

Solifenacin

Efficacy of Solifenacin

One 12-week, double-blind, trial compared solifenacin 3 (n=43), 6 (n=43), or 9 mg (n=44) doses daily to placebo (n=92) in men with LUTS and OAB symptoms.[42] Individuals with a baseline post void residual of >200 ml were excluded. Mean age was 65 and mean baseline I-PSS score was 18.5. Nearly all men were white. This industry-sponsored trial was conducted in several sites in Europe. Risk of bias was moderate.

None of the solifenacin doses were superior to placebo in improving I-PSS scores (MD for 6 mg) = -0.30; 95% CI: -1.74 to 2.34) (insufficient SOE). Urinary retention requiring catheterization was reported in one participant allocated to solifenacin 9 mg.

Overall withdrawals and withdrawal due to adverse effects were similar with solifenacin and placebo. Dry mouth was reported more often with solifenacin (6 percent) versus placebo (0 percent).

Efficacy of Solifenacin AB Combination

Three double-blind 12-week trials (n=1857) compared a solifenacin-AB combination with placebo (Table 7).[42,43,45] Trials combined solifenacin doses of 3, 6, or 9 mg with tamsulosin 0.4 mg. Two studies excluded patients with baseline PVRs >150[43] or >200 ml,[42] respectively. Mean age of participants was 66 and mean baseline I-PSS score was 18.3 (range 17.8 to 18.6). Participants were predominantly white (99 percent). Two trials were conducted in Europe and one in Europe and the United States. All were industry-sponsored and had lowrisk of bias. .

Mean change in I-PSS scores was larger with solifenacin-AB combination than placebo (WMD = -1.5; 95% CI: -2.3 to -0.70) (moderate SoE). Mean reduction in I-PSS scores with combination was 7.3 points compared with 4.0 points with placebo. The magnitude of effect of combination therapy with 9 mg solifenacin appeared lower than with 6 mg. Combination therapy achieved a greater reduction in I-PSS QoL scores than placebo (low SoE). Among the three trials, 11 cases of urinary retention were reported with combination therapy and none with placebo.

Withdrawal for any reason was similar with combination therapy and placebo (low SoE). Withdrawal due to adverse effects and the proportion of participants reporting ≥1 adverse effect were higher with combination therapy than placebo (moderate SoE). Combination therapy was more likely to cause dry mouth and constipation than placebo.

Table 7. Evidence overview: solifenacin/AB combination versus placebo

Solifenacin, 6 mg Plus AB vs. Placebo *(3 RCT[42,43,45]; N=1857)*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Placebo Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	3 (1023)	-7.3	-5.7	Favors combination (6 mg) WMD=-1.50 [-2.30 to -0.70]	Moderate (moderate study limitations)
I-PSS QoL, *mean change from baseline*	1 (629)	-1.3	-0.9	Favors combination WMD=-0.40 [-0.70, -0.10]	Low (moderate study limitations, unknown consistency)
Overall withdrawals	3 (1857)	9% (127/1350)	8% (42/507)	EQUIVALENT RR=1.20 [0.76 to 1.89]	Low (moderate study limitations, imprecise)
Withdrawals due to adverse effects	3 (1857)	4% (50/1350)	2% (8/507)	Greater with Combined RR=2.17 [1.04 to 4.55] ARD = 0.03 [0.01 to 0.04] NNH = 34	Moderate (moderate study limitations)
Participants with ≥1 adverse effect	3 (1848)	28 (378/1341)	25 (128/507)	Greater with Combined RR = 1.24 [1.04 to 1.47] ARD = 0.06 [0.02 to 0.10] NNH = 17	Moderate (moderate study limitations)

ARD=absolute risk difference; CI=confidence intervals; I-PSS=International Prostate Symptom Score; ND=No statistically significant difference; NNH=number needed to harm; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Efficacy of Solifenacin Added to AB Monotherapy

Seven trials[40-43,48,49,53] with 3147 participants contributed to the analysis of solifenacin plus tamsulosin versus tamsulosin monotherapy (Table 8). Participants had a mean age of 66 years and a mean I-PSS score of 17.2 (range of mean I-PSS scores: 13.5 – 19.4) at baseline; and 96 percent were white. Five trials examined solifenacin, 5 mg[40,41,48,49,53] and two examined 6 mg.[42,43] Dosage of tamsulosin varied geographically. Three studies were conducted in South Korea[40,41,49] and one in Japan;[48] these trials used a daily 0.2 mg tamsulosin dose. One trial was conducted in the United States[53] and two in Europe;[42,43] these trials used a daily 0.4 mg tamsulosin dose. All trials except one[49] reported industry sponsorship; Seo et al. did not report a funding source. Overall risk of bias was moderate.

Six trials assessed IPSS score. Improvement in mean I-PSS score from baseline was similar with solifenacin 5 or 6 mg plus tamsulosin 0.2 or 0.4 mg versus tamsulosin alone (WMD: -0.29; 95% CI: -0.74 to 0.16) (moderate SoE). Four trials using solifenacin 5 mg[40,48,49] or 6 mg[43] showed that combination therapy lowered I-PSS QoL score more than tamsulosin (WMD: -0.18; 95% CI: -0.34 to -0.02) (moderate SoE), but the difference is less than the MDD. Four trials using solifenacin 3 to 9 mg[42,43,48,49,53] show higher AUR with combination therapy than

monotherapy (RR: 3.75; 95% CI: 95% 1.11-12.69) (low SoE). No other indicators of disease progression/treatment failure were reported.

Withdrawal for any reason or due to adverse effects was similar with both treatments (low SoE). More participants reported one or more adverse effects with combination treatment than monotherapy (moderate SoE). Combination therapy was more likely than placebo to cause dry mouth and constipation.

Table 8. Evidence overview: solifenacin/AB combination versus AB monotherapy

Solifenacin, 5 or 6 mg Plus AB vs. AB *7 RCT*[40-43,48,49,53]*; N=3639)*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	6 (1948)	-5.8	-5.4	EQUIVALENTWMD=-0.29 [-0.74, 0.16]	Moderate (moderate study limitations)
I-PSS QoL, *mean change from baseline*	4 (1225)	-1.2	-0.9	Favors Combination WMD=-0.18 [-0.34, -0.02]	Moderate (moderate study limitations)
Acute urinary retention	4 (2531)	1% (21/1615)	1% (2/916)	Greater with Combination RR=3.75 [1.11, 12.69] ARD = 0.01 [-0.00 to 0.02]	Low (moderate study limitations, imprecise)
Overall withdrawals	7 (3147)	10% (203/2028)	11% (121/1119)	EQUIVALENTRR=1.02 [0.78, 1.33]	Low (moderate study limitations imprecise)
Withdrawals due to adverse effects	5 (2900)	4% (71/1904)	3% (30/996)	EQUIVALENTRR=1.27 [0.84, 1.95]	Low (moderate study limitations, imprecise)
Participants with ≥1 adverse effect	5 (2918)	33% (623/1913)	29% (280/1005)	Greater with Combination RR=1.21 [1.08, 1.36] ARD = 0.05 [0.02 to 0.09] NNH = 20	Moderate (moderate study limitations

ARD=absolute risk difference; CI=confidence intervals; I-PSS=International Prostate Symptom Score; ND=no statistically significant difference; NNH=number needed to harm; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Long-term Adverse Effects

We identified one study examining long-term adverse effects associated with solifenacin-AB combination therapy.[99] A select subset of participants from a previous RCT could participate in the 40-week open-label extension study (n=1066). Participation was limited to those with storage and voiding LUTS, maximum flow of 4.0 to 12. 0 ml/s, prostate size <75 ml, and postvoid residual ≤150 ml. Among participants in the extension,. 47 percent of participants reported treatment-emergent adverse effects. Dry mouth, constipation, and dyspepsia were the most common long-term adverse effects. Among 1066 patients, 86 serious adverse effects occurred in 64 patients and included 3 deaths, 6 cases of AUR (0.7 percent), and 3 cases of intervertebral disc protrusion.

Fesoterodine

Efficacy of Fesoterodine Added to AB Monotherapy

Two trials (n=990) compared fesoterodine/AB combination therapy with AB monotherapy (Table 9).[44,51] Mean age was 66 and mean baseline I-PSS score was 18.9 (range 16 to 19). Most participants were white (81 percent) in one trial that reported race/ethnicity.[51] Participants were randomized to daily doses of fesoterodine 4 mg combined with various ABs (most frequently

tamsulosin) vs the AB alone. One trial (n=943) was multinational[51] and the other (n=47) was conducted in Greece.[44] One trial reported industry sponsorship[51] and the other did not report sponsorship.[44] Overall risk of bias was moderate for one trial[51] and high for the other.[44]

Improvement in mean I-PSS scores was similar with fesoterodine-AB combination and AB monotherapy (WMD = -0.07; 95% CI: -0.88 to 0.75) (low SoE). AUR was infrequent in the one study that reported this outcome (≤1 percent) and only one participant in each study arm required catheterization.[51] Konstantinidis et al. did not report AUR.[44]

Withdrawal for any reason, withdrawal due to adverse effects, and reporting at least one adverse effect was more frequent with combination treatment than with monotherapy. Dry mouth and constipation were more frequent with combination therapy than monotherapy.

Table 9. Evidence overview: fesoterodine/AB combination versus AB monotherapy

Fesoterodine 4 mg vs. AB monotherapy *(2 RCT[44,51]; N=990)[a]*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	2 (990)	-4.3	-4.2	EQUIVALENTWMD = -0.07 [-0.88 to 0.75]	Low (moderate study limitations and consistency[a])
AUR	1 (947)	0.2 (1/474)	0.2 (1/473)	EQUIVALENTRR 1.00 [0.06 to 15.91]	Insufficient (moderate study limitations, imprecise, unknown consistentcy)
Overall withdrawals	1 (947)	15 (73/474)	10 (49/473)	Greater with fesoterodine RR 1.49 [1.06 to 2.09] ARD = 0.05 [0.01 to 0.09] NNH =20	Low (moderate study limitations and unknown consistency)
Withdrawals due to adverse effects	1 (947)	10 (46/474)	4 (20/473)	Greater with fesoterodine RR = 2.30 [1.38 to 3.82] ARD = 0.05 [0.01 to 0.09] NNH =20	Low (moderate study limitations and unknown consistency)
Participants with ≥1 adverse effect	1 (947)	49 (230/474)	33 (157/473)	Greater with fesoterodine RR = 1.46 [1.25 to 1.71] ARD = 0.15 [0.09 to 0.22] NNH = 7	Low (moderate study limitations and unknown consistency)

ARD=absolute risk difference; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NNH=number needed to harm; t;; RR=risk ratio;; WMD=weighted mean difference
a One trial was small (n=47) and contributed little weight to the estimate

Oxybutynin

Efficacy of Oxybutynin Added to AB Monotherapy

One 12-week double-blind trial (N=420) trial compared oxybutynin and AB combination therapy with AB monotherapy.[55] Individuals with a baseline post void residual of >200 ml were excluded. Mean age of the participants was 63 and mean baseline I-PSS score was 20. Most participants were white (90 percent). Participants were randomized to daily doses of oxybutynin 10 mg combined with tamsulosin 0.4 mg versus placebo with tamsulosin 0.4 mg monotherapy. The trial, conducted in the United States, reported industry sponsorship. Risk of bias was moderate.

Oxybutynin-AB combination therapy was superior to AB monotherapy in improving mean I-PSS scores (WMD = -1.70; 95% CI: -2.93 to -0.47) (low SoE).

Rates of total withdrawals, withdrawal due to adverse effects, and proportions of participants with ≥1 AE were similar with oxybutynin-AB combination therapy and AB monotherapy (insufficient to low SoE).

Darifenacin

Efficacy of Darifenacin Added to AB Monotherapy

One 12-week, double-blind, trial (n=101) compared darifenacin 7.5 mg with doxazosin 4 mg combination therapy to AB monotherapy (doxazosin 4 mg) in men with LUTS and OAB symptoms.[47] Individuals with a baseline post void residual of >150 ml were excluded. Mean age was 64 and mean baseline I-PSS score was 16.3. This trial was conducted in Turkey. Funding was not reported. Risk of bias was moderate.

The information provided was insufficient to assess efficacy(insufficient evidence). No withdrawals or adverse effects were reported.

Trospium

Efficacy of Trospium Added to AB Monotherapy

One double-blind 12-week trial (n=58) compared trospium 45 mg daily doses with AB to AB monotherapy in men with LUTS and OAB symptoms.[46] Individuals with a baseline post void residual of >100 ml were excluded. Mean age was 58 and mean baseline I-PSS score was 15.3. This trial was conducted in Turkey. Sponsorship was not reported. Risk of bias was moderate.

The information provided was insufficient to assess efficacy for any outcome (insufficient evidence). Rates of total withdrawals were not reported. One or more adverse effects were reported in nine (35 percent) trospium participants versus five (23 percent) placebo patients.

Beta 3 Agonists

Supporting tables relevant to beta-3 agonists appear in Appendix F.

Key Points

- Evidence was insufficient to assess efficacy or adverse effects of mirabegron compared with placebo.
- Evidence was insufficient to assess comparative effectiveness or adverse effects of mirabegron-AB combination therapy compared with AB monotherapy.
- No studies assessed longer-term treatment harms.

Mirabegron

Efficacy of Mirabegron

One trial (n=200)[63] assessed the efficacy of mirabegron at 50 mg (n=70) and 100 mg doses (n=65) with placebo (n=65) in males with LUTS/BPH. The study enrolled patients with I-PSS ≥8, was conducted in the United States and Canada and was funded by industry. Mean age of participants was 63. The study had low risk of bias.

Mean I-PSS score changes in the 50 mg, 100 mg and placebo groups were -6.2, -4.2 and -0.5. The information provided was insufficient for effect size calculation or pooling across dose levels for any outcome or adverse effect (insufficient evidence).

Efficacy of Mirabegron Added to AB Monotherapy

One trial[62] (n=94) compared 50 mg of mirabegron combined with 0.2 mg tamsulosin versus 0.2 mg tamsulosin monotherapy in males with LUTS/BPH and OAB. All patients were pretreated with tamsulosin. Patients with a PVR >100 ml were excluded; mean age was 75. The study had high risk of bias (open label). Mean change in I-PSS score was similar with combination therapy and monotherapy (insufficient evidence). Adverse effects were also similar (insufficient evidence).

PDE-5s

Supporting tables and figures relevant to PDE-5s appear in Appendix G.

Key Points

- Tadalafil improves LUTS attributed to BPH more than placebo over the short-term. Effect size is small and adverse effects are more frequent with tadalafil.
- Tadalafil combined with AB improves LUTS attributed to BPH more than AB monotherapy over short-term treatment. Effect size is small. Evidence is insufficient to assess comparative adverse effects.
- Tadalafil 5mg and tamsulosin are similarly effective in treating LUTS over the short-term. Rates of adverse effects are similar.
- Observational studies show high rates of adverse effects during longer term treatment with tadalafil.
- No studies assessed long-term efficacy or AEs of any PDE-5.

Tadalafil

Efficacy of Tadalafil

Ten eligible trials randomized men with LUTS attributed to BPH (n=3516) to tadalafil versus placebo, with all trials lasting 3 months (Table 10).[64,68,71,73,77-79,81,84,85] Mean age of the participants was 63 and mean baseline I-PSS score was 17.5 (range 16.4 to 21.8). In the five trials that reported race/ethnicity, most participants were white (86 percent).[73,77,78,81,84] Approximately 75 percent of participants had ED history. All participants in Egerdie et al. were sexually active and had BPH-LUTS and ED.[77] The dose of tadalafil used most frequently was 5 mg daily (seven trials); followed by 2.5 mg tadalafil (three trials). One trial was a dose finding study, evaluating doses of 2.5, 5, 10, and 20 mg[84] and others evaluated 20 mg doses.[81,85] Four trials were multinational studies,[73,77,78,84] one was conducted in the United States and Canada,[81] one in the United States and four were conducted in Asia. [64,68,71,79,85] All trials reported industry sponsorship and had low to moderate overall risk of bias.

One trial conducted a responder analysis, defined as a ≥3 point reduction from baseline I-PSS score.[85] Forty-nine percent responded with tadalafil compared with 36 percent with placebo, a 13 percent increase in absolute risk difference (low SoE). Tadalafil 5 mg improved mean I-PSS scores from baseline more than placebo (WMD = -1.8; 95% CI: -2.4 to -1.4) (moderate SoE).

Tadalafil improved I-PSS scores by 5.5 points compared with 3.4 points with placebo. Both treatments reduced I-PSS scores by MDD. Tadalafil 10 mg daily (WMD = -2.9; 95% CI: -4.3 to -1.5; n=1 trial[84]) and tadalafil 20 mg daily (WMD = -3.3; 95% CI: -4.4 to -2.1; n=2 trials[81,84]), showed larger effect sizes suggesting a dose-response relationship (test for subgroup differences I^2=76 percent, p=0.006). Seven trials reported BII. Tadalafil 5 mg improved BII scores more than placebo (WMD -0.52; 95% CI: -0.74 to -0.30), with both treatments showing improvements greater than MDD (-1.7 with tadalafil and -1.1 with placebo). The WMD above the MDD indicates that most will see important benefits from tadalafil 5 mg. Tadalafil at 2.5 mg or 10 mg was similar to placebo in improving BII scores (insufficient evidence). I-PSS QoL improved more with tadalafil than placebo (WMD = -0.27; -0.38 to -0.17) (moderate SoE). Mean changes from baseline were -1 and -0.7 points with tadalafil and placebo. Incidence of AUR was rare, reported in two participants with placebo in two trials. No other indicators of disease progression/treatment failure were reported.

Study withdrawal for any reason was similar with tadalafil 5 mg and placebo (moderate SoE). However, participants allocated to tadalafil 5 mg were more likely to withdraw due to an adverse effect; the absolute difference was small, one percent (high SoE). The proportion of withdrawals due to adverse effects increased at higher doses but the differences between doses was not significant. The proportion reporting at least one adverse effect was higher with tadalafil 5 mg than placebo, 29 percent versus 22 percent (high SoE). A higher proportion of adverse effects at higher doses indicated a dose-response relationship (I^2=76 percent, p=0.006), but only three trials evaluated doses greater than 10 mg.[81,84,85] Four trials reported that dyspepsia was an adverse effect associated with tadalafil use (3 percent vs. 0 percent for placebo).[71,73,81,84] Short-term, serious adverse effects were rare and reported in similar proportions with tadalafil and placebo (approximately 1 percent each). Three myocardial infarction deaths were reported in three trials, two with tadalafil,[77,78] and one with placebo.[81]

Table 10. Evidence overview: tadalafil versus placebo

Tadalafil 5 mg vs. Placebo *(10 RCT*[64,68,71,73,77-79,81,84,85]*; N=3516*[a]*)*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Placebo Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	9 (3024)	-5.5	-3.4	Favors tadalafil WMD = -1.79 [-2.21 to -1.37]	Moderate (imprecise)
BII, *mean change from baseline*	7 (2161)	-1.7	-1.1	Favors tadalafil WMD = -0.52 [-0.74 to -0.30]	Moderate (imprecise)
I-PSS QoL, *mean change from baseline*	8 (2605)	-1.0	-0.7	Favors tadalafil WMD = -0.27 [-0.38 to -0.17]	High
Overall withdrawals	9 (3082)	10.5 (115/1098)	10.5 (115/1093)	EQUIVALENTRR 1.00 [0.80 to 1.26]	Moderate (imprecise)
Withdrawals due to adverse effects	9 (3082)	3.4 (37/1098)	1.6 (17/1093)	Greater with tadalafil RR = 1.80 [1.07 to 3.04 ARD = 0.01 [0.00 to 0.03] NNH =100	High
Participants with ≥1 adverse effect	9 (3082)	28.7 (315/1098)	22.0 (240/1093)	Greater with tadalafil RR = 1.25 [1.10 to 1.42] ARD = 0.07 [0.03 to 0.10] NNH = 15	High

; ARD=absolute risk difference; BII=Benign prostatic hyperplasia Impact Index; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; NNH=number needed to harm; NNT=number needed to treat; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Long-term Adverse Effects

Because no RCTs reported intermediate or long-term harms (i.e., follow-up longer than 3 months), we extracted longer term harms data from observational studies. Takeda, et al. conducted a 42-week, open-label extension study after the 3-month RCT in which all participants took tadalafil 5 mg daily.[71] Nearly 59 percent of the 394 participants reported at least one adverse effect and 9 percent withdrew due to an adverse effect. Adverse effects were similar to those reported during the double-blind phase. Serious adverse effects were reported in 3 percent (11 participants) with the most serious adverse effects being urinary retention requiring catheterization in one participant and the death from a subarachnoid hemorrhage in another.

Donatucci et al. conducted a 1-year open-label extension study in which participants continued once-daily tadalafil 5 mg.[103] Of the 886 participants completing the 12-week trial, 427 elected to continue and 299 completed the extension study. Nearly 5 percent experienced serious adverse effects and 58 percent experienced adverse effects that first occurred or worsened during the extension. Only 2 of the 20 serious adverse effects, those considered drug-related by investigators, were described (worsening of coronary artery disease and global amnesia). Common adverse effects included dyspepsia (4 percent), gastro-oesophageal reflux disease (4 percent), back pain (4 percent), sinusitis (3 percent), hypertension (3 percent), and cough (2 percent).

Patient Demographic and Clinical Characteristics

Evidence from one RCT (n=175),[78] and a posthoc analysis of a previous trial (n=1056),[97] shows no difference in the effect of tadalafil 5 mg based on presence or severity or ED. Evidence from one pooled analysis (n=1500)[94] and one RCT (n=302) shows no difference in the effect of tadalafil 5 mg based on LUTS severity. Evidence from one pooled analysis (n=1500) shows no difference in the effect of tadalafil 5 mg based on age, previous use of ABs, or previous use of PDE-5s. Evidence from one RCT (n=510) shows no difference in the effects of tadalafil or placebo based on previous use of ABs.[73]

Efficacy of Tadalafil Added to AB Monotherapy

Four trials randomized males with BPH (n=216) to tadalafil combined with an AB or to AB monotherapy (Table 11).[65,66,69,82] Two 3-month trials compared tadalafil 10 mg daily[66] or 20 mg on alternate days[82] combined with alfuzosin 10 mg to alfuzosin 10 mg monotherapy. Two trials evaluated tadalafil combined with tamsulosin 0.4 mg vs tamsulosin 0.4 mg monotherapy: a 1-month trial evaluated tadalafil 5 mg daily[69] and a 4-month trial evaluated tadalafil 10 mg daily.[65] Mean age of the participants was 61 and mean baseline I-PSS score was 19.4 (range 15.5 to 21.3). Nearly all participants had ED history.[65,66,82] Trials were conducted in India,[65,66] Italy,[82] and Brazil.[69] All trials were open-label except Regadas et al.[69] and overall risk of bias therefore ranged from moderate to high.

Tadalafil 5-20 mg combined with AB was superior to AB monotherapy in improving mean I-PSS scores from baseline (WMD = -2.0; 95% CI: -3.3 to -0.8), indicating that an appreciable number may benefit from combination therapy (low SoE).[65,66,69,82] Mean reductions in I-PSS scores were 10.4 and 8.6 with combination and monotherapy. Both treatments reduced mean I-PSS scores by MDD. Improvement in mean I-PSS QoL scores was also higher with combination treatment than monotherapy, however only open label (high risk of bias) trials reported this outcome (low SoE).

Withdrawals and withdrawals due to adverse effects were similar with combination and monotherapy (insufficient evidence).

An additional double-blinded trial conducted in the United States (n=318) enrolled males already receiving stable AB therapy for LUTS and randomized them to tadalafil 5 mg or placebo, while continuing their AB therapy.[75] Mean age was 67 and baseline I-PSS score was 13.6. Mean change in I-PSS scores from baseline was similar with combination therapy and monotherapy in men already receiving AB monotherapy at enrollment.[75] There were no differences in withdrawals or withdrawals due to adverse effects, and no serious adverse effects were reported.

Table 11. Evidence overview: combined tadalafil/AB versus AB monotherapy

Tadalafil 5-20 mg Plus AB vs. AB Monotherapy(4 RCT[65,66,69,82]; N=216)	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	4 (214)	-10.4	-8.6	Favors combined WMD = -2.02 [-3.26 to -0.77]	Low (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	3 (174)	-3.7	-3.3	Favors combined WMD = -0.44 [-0.61 to -0.26]	Low (high study limitations, imprecise)
Overall withdrawals	4 (224)	4 (5/112)	5 (6/112	EQUIVALENT RR = 0.80 [0.25 to 2.50]	Insufficient (high study limitations, very imprecise)
Withdrawals due to adverse effects	4 (224)	4 (4/112)	3 (3/112	EQUIVALENT RR = 1.13 [0.29 to 4.33]	Insufficient (high study limitations, very imprecise)

; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Efficacy of Tadalafil Added to 5ARI Monotherapy or 5ARI/AB Combination

One 26-week, double-blind trial (n=696) compared combined tadalafil 5 mg and finasteride 5 mg daily vs placebo and finasteride 5 mg daily.[67] Mean age was 64 and mean baseline I-PSS score was 17.3. Most participants were white (86 percent) and had ED history (65 percent). The trial had sites in the United States, Latin America, and Europe. The trial reported industry sponsorship, and overall risk of bias was low.

Combined tadalafil/finasteride therapy improved mean I-PSS scores more than finasteride monotherapy (MD = -1.0; 95% CI: -1.9 to -0.2) (low SoE). Combined therapy improved I-PSS scores by 5.5 points compared with 4.5 points with finasteride monotherapy. I-PSS QoL improvement was similar with combination and monotherapy (MD = -0.2; 95% CI: -0.4 to 0.0) (low SoE). Mean changes from baseline were -1.1 and -0.9 points with combination and monotherapy, respectively. Study withdrawal for any reason was greater with finasteride monotherapy compared with combination therapy (low SoE). Withdrawals due to adverse effects were infrequent but similar between the groups (insufficient evidence). The proportion reporting at least one adverse effect was not significantly different between treatment groups (insufficient evidence). Two participant deaths were reported, one each in the combined (metastatic pancreatic carcinoma) and finasteride/placebo (cerebrovascular accident) arms. Erectile dysfunction as an adverse effect was reported in five finasteride/placebo participants compared with one combined therapy patient.

One 3-month trial (n=132) evaluated combined tadalafil 10 mg daily with “standard therapy” for BPH defined as either an AB or finasteride versus placebo with “standard therapy” for BPH.

.[74] Mean age was 65 and mean baseline I-PSS score was 13.4. The trial was conducted in Iran. Industry sponsorship was not reported and risk of bias was moderate.

Combined tadalafil/standard therapy improved mean I-PSS scores more than standard therapy/placebo (MD = -3.1; 95% CI: -4.5 to -1.7) (insufficient evidence). Combined tadalafil/standard therapy improved I-PSS scores by 5.4 points compared with 2.3 points with standard therapy/placebo. Combined tadalafil/standard therapy also improved I-PSS QoL scores more than standard therapy/placebo (MD = -0.6; 95% CI: -0.9 to -0.3). Mean changes from baseline were -1.1 and -0.5 points with combined tadalafil/standard therapy and standard therapy/placebo.

Six and four participants in the combined tadalafil/standard therapy and standard therapy placebo groups withdrew from the trial due to adverse effects (insufficient evidence)

Comparative Effectiveness of Tadalafil Versus Tamsulosin

Four 3-month trials compared tadalafil 2.5, 5 or 10 mg daily with tamsulosin 0.2or 0.4 mg daily (Table 12).[65,68,73,79] Mean age was 63 and mean baseline I-PSS score was 17.4 (range 16.8 to 20.6). Most participants were white (77 percent) in one multinational trial reporting race/ethnicity.[73] Most participants had ED history.[65,73,79] The most frequently investigated dose level of tadalafil was 5mg; one trial studied a 2.5 mg dose.[68,73,79] and one trial evaluated10 mg.[65] Two trials conducted in Japan and Korea allocated participants to tamsulosin 0.2 mg daily.[68,79] The multinational trial[73] and the Indian trial evaluating tadalafil 10 mg[65] allocated participants to tamsulosin 0.4 mg. Three trials reported industry sponsorship.[68,73,79] Overall risk of bias was low to high for the four trials; Singh was open-label.[65]

Tadalafil 5 mg and tamsulosin were similar in improving mean I-PSS scores (WMD = 0.07; 95% CI: -0.88 to 1.02) (moderate SoE), BII, and I-PSS QoL (low SoE).

Study withdrawal for any reason, withdrawal due to adverse effects, and proportion of participants reporting at least one adverse effect was similar with tadalafil or tamsulosin (insufficient evidence). Kim et al. reported two subjects in each treatment arm reported serious adverse events: pleural effusion with metastatic lung adenocarcinoma and lumbar spinal stenosis with tadalafil and acute myocardial infarction and inguinal hernia with tamsulosin.[79] Yokoyama et al reported four serious adverse effects with tadalafil (colon cancer with metastatic liver carcinoma, hospitalization because of injury, hypertension, lumbar spinal stenosis) and one with placebo (malignant lymphoma).[68] Oelke et al. reported two serious adverse effects with each treatment.[73] Singh et al. reported that no serious adverse effects occurring during the study period.[65]

Table 12. Evidence Overview: tadalafil versus tamsulosin

Tadalafil 5 mg vs. Tamsulosin 0.2-0.4mg *(3 RCT[68,73,79]; N=)*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**ControlMean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	3 (742)	-5.6	-5.9	EQUIVALENTWMD = 0.07 [-0.88 to 1.02]	Moderate (moderate study limitations)
BII, *mean change from baseline*	3 (731)	-1.5	-1.5	EQUIVALENTWMD -0.02 [-0.70 to 0.66]	Insufficient (moderate study limitations, imprecise, inconsistent)
I-PSS QoL, *mean change from baseline*	3 (742)	-1.1	-1.1	EQUIVALENTWMD = -0.01 [-0.38 to 0.37]	Low (moderate study limitations, inconsistent)
Overall withdrawals	3 (742)	9.7 (36/373)	7.6 (28/369)	NS RR = 1.35 [0.64 to 2.85]	Low (moderate study limitations, imprecise)

Withdrawals due to adverse effects	3 (742)	2.9 (11/373)	1.1 (4/369)	EQUIVALENTRR = 2.68 [0.85 to 8.39]	Insufficient (moderate study limitations, very imprecise)
Participants with ≥1 adverse effect	3 (742)	25.2 (94/373)	24.4 (90/369)	EQUIVALENTRR = 0.99 [0.67 to 1.46]	Low (moderate study limitations, imprecise)

BII=Benign prostatic hyperplasia Impact Index; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Patient Demographic and Clinical Characteristics

One trial (n=510) assessed response to treatment by whether ABs had been used previously. There was no difference in the effects of tadalafil or tamsulosin according to previous use of ABs.[73]

Comparative Effectiveness of Tadalafil Versus Alfuzosin

Two 3-month trials (n=93) compared tadalafil with alfuzosin 10 mg daily (Table 13).[66,82] Neither trial evaluated the FDA approved dose level of 5 mg of tadalafil but studied higher doses. Kumar et al. compared tadalafil 10 mg daily with alfuzosin 10 mg daily.[66] Liguori et al. compared tadalafil 20 mg taken on alternate days with alfuzosin 10 mg daily.[82] Mean age of the participants was 61 and mean baseline I-PSS score was 16.2 (range 14.7 to 17.3). All participants had a history of ED. Trials were conducted in India[66] and Italy.[82] Neither trial reported sponsorship. Both trials were open-label with high overall risk of bias.

Alfuzosin 10 mg improved mean I-PSS scores more than tadalafil 10 or 20 mg (WMD = 3.3; 95% CI: 2.0 to 4.7) (low SoE). Mean reductions in I-PSS scores were 4.1 and 7.2 points with tadalafil and alfuzosin, respectively. I-PSS QoL also improved more with alfuzosin than tadalafil (low SoE).

Study withdrawal for any reason and withdrawal due to an adverse effect were similar with tadalafil and alfuzosin (insufficient evidence). Liguori et al. reported one participant discontinued treatment with tadalafil (back pain, headaches) versus three with alfuzosin (dizziness, constipation).[82] Kumar et al. reported two participants developed occasional headaches with tadalafil.[66] No serious adverse effects were reported.

Table 13. Evidence Overview: tadalafil versus alfuzosin

Tadalafil 10-20 mg vs. Alfuzosin 10 mg *(2 RCT[66,82]; N=93)*	**# Trials (n)**	**Treatment Mean or % (n/N)**	**Control Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	2 (87)	-4.1	-7.2	Favors alfuzosin WMD = -3.33 [1.98 to 4.68]	Low (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	2 (87)	-1.8	-2.4	Favors alfuzosin WMD = -0.61 [0.13 to 1.08]	Low (high study limitations, imprecise)
Overall withdrawals	2 (93)	4 (2/46)	9 (4/47)	EQUIVALENTRR = 0.52 [0.11 to 2.56]	Insufficient (high study limitations, imprecise)
Withdrawals due to adverse effects	2 (93)	4 (2/46)	9 (4/47)	EQUIVALENTRR = 0.35 [0.04 to 3.10]	Insufficient (high study limitations, imprecise)

; CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Efficacy of Sildenafil

One 3-month trial (n = 369) compared sildenafil 50 mg (increasing to 100 mg at 2 weeks) with placebo.[86] Participants could return to the 50 mg dose if the 100 mg dose was not tolerated. Baseline mean I-PSS score was not reported, but a minimum of 12 was required for enrollment. Mean age was 60 and most participants were white (82 percent); all were experiencing ED in addition to LUTS/BPH. The trial was conducted in the United States, reported industry sponsorship and had low overall risk of bias.

Sildenafil 50 to 100 mg improved I-PSS scores more than placebo (MD -4.4; 95% CI: -6.9 to -1.9) indicating that most participants achieved meaningful benefits (insufficient evidence). Mean change from baseline was -6.3 with sildenafil and -1.9 with placebo. BII mean change was also greater with sildenafil (-2.0 points) than placebo (-0.9 points). Mean change in I-PSS QoL was larger with sildenafil than placebo, -1.0 and -0.3.

Sildenafil and placebo had similar study withdrawals for any reason, withdrawals due to adverse effects, and proportion reporting one or more adverse effects (insufficient evidence). Headache and dyspepsia were reported more frequently with sildenafil than placebo (11 percent vs. 3 percent and 6 percent vs. 1 percent, respectively). Two serious adverse effects were reported with sildenafil, including one severe acute cerebrovascular stroke.

Patient Demographic and Clinical Characteristics

One posthoc analysis of a previous trial (n=341) reported no difference in the effect of sildenafil based on baseline BMI or LUTS severity.[98]

Efficacy of Sildenafil Added to AB Monotherapy

Four trials (n=281) compared sildenafil combined with an AB with AB monotherapy (Table 14).[70,72,80,87] The combinations studied varied. Two 3-month trials evaluated sildenafil combined with alfuzosin 10 mg, one used daily sildenafil 25 mg,[87] the other sildenafil 50 mg (dosing frequency not reported).[72] One 4-month trial evaluated sildenafil 50 mg combined with doxazosin 2 mg but the frequency of administration was not reported.[70] An 8-week trial evaluated sildenafil 25 mg taken 4 days per week combined with tamsulosin 0.4 mg daily.[80] Mean age of the participants was 61 and mean baseline I-PSS score was 17.7 points (range 15.6 to 19.9). Three trials enrolled males with a history of ED.[70,80,87] Trials were conducted in Egypt,[70] Turkey,[72,80] and the United States.[87] The U.S. trial reported industry sponsorship and the Egyptian trial reported receiving no support. All trials were open label or otherwise inadequately blinded and enrolled patients after they failed to respond to AB monotherapy. Overall risk of bias was mostly high.

Mean I-PSS scores improved more with combination than monotherapy (WMD = -1.7; 95% CI: - 3.1 to -0.4) (insufficient evidence).[70,72,87] Mean reductions in I-PSS scores were 5.4 with combination and 3.9 with monotherapy, both treatments exceeding MDD. In the trial without data sufficient for pooling, improvement in mean I-PSS scores was similar with combination or monotherapy (-6.4 vs. -5.4) and over 8 weeks.[80] Improvement in I-PSS QoL was also similar with combination versus monotherapy (insufficient evidence). [72,80]

Overall withdrawals and withdrawals due to adverse effects were similar with combination and AB monotherapy (insufficient evidence). Kaplan et al. reported three participants withdrew due to gastric upset and dizziness with combination therapy and two withdrew due to dizziness with alfuzosin.[87] No serious adverse effects were reported. Abolyosr et al. reported slight

dizziness and blurring of vision, mainly in participants who took combined therapy.[70] Tuncel et al. did not report withdrawals or adverse effects.[80]

Table 14. Evidence overview: sildenafil/AB combination versus AB monotherapy

Sildenafil + AB vs. AB *(4 RCT[70,72,80,87]; N=281)*	# Trials (n)	Treatment Mean or % (n/N)	Control Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
I-PSS score, *mean change from baseline*	4 (273)	-5.4	-3.9	Favors combined WMD = -1.73 [-3.11 to -0.35]	Insufficient (high study limitations, imprecise)
		-6.4	-5.4	EQUIVALENTMD = -1 [CI NR]	Insufficient (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	2 (132)	-1.9	-1.4	EQUIVALENT WMD = -0.65 [-1.73 to 0.42]	Insufficient (high study limitations, imprecise inconsistent)
Overall withdrawals	2 (141)	11 (8/71)	7 (5/70)	EQUIVALENT RR = 1.57 [0.54 to 4.55]	Insufficient (high study limitations, imprecise)
Withdrawals due to adverse effects	2 (141)	4 (3/71)	3 (2/70)	EQUIVALENT RR = 1.43 [0.27 to 7.67]	Insufficient (high study limitations, imprecise)

CI=confidence intervals; I-PSS=International Prostate Symptom Score; NS=no statistically significant difference; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Comparative Effectiveness of Sildenafil Versus AB

Three trials (n=181) compared sildenafil versus an AB (Table 15).[70,80,87] One compared sildenafil 25 mg daily with alfuzosin 10 mg daily over 3 months[87] and compared sildenafil 25 mg taken 4 days per week with tamsulosin 0.4 mg daily over 8 weeks.[80] Abolyosr et al. compared sildenafil 50 mg with doxazosin 2 mg over 4 months; frequency of administration was not reported. Mean age of the participants was 61[80,87] and mean baseline I-PSS was 16.3 (range 14.9 to 17.1). All participants had ED history. Trials were conducted in Egypt,[70] Turkey,[80] and the United States.[87] The U.S. study reported industry sponsorship and the Egyptian trial reported receiving no support. All trials were open label and overall risk of bias was high.

Sildenafil 25 to 50 mg was similar to alfuzosin 10 mg and doxazosin 2 mg in improving mean I-PSS scores.[70,87] Mean reduction in I-PSS scores was -2.2 with sildenafil and -3.2 with alfuzosin or doxazosin. In data available from one trial not pooled, tamsulosin 0.4 mg improved mean I-PSS scores more than sildenafil 25 mg (insufficient evidence).[80] Mean reduction with sildenafil was 4 points versus 5.4 points for tamsulosin. I-PSS QoL improved more with sildenafil than tamsulosin (insufficient evidence).[80 2010]

Overall withdrawals and withdrawals due to adverse effects were similar with sildenafil and AB monotherapy (insufficient evidence). Kaplan et al. reported two participants using sildenafil withdrew due to flushing and dyspepsia and two using alfuzosin withdrew with dizziness.[87] Abolyosr et al. and Tuncel et al. did not report withdrawals.[70,80]

Table 15. Evidence Overview: sildenafil versus AB Monotherapy

Sildenafil 25-50 mg vs. AB (3 RCT[70,80,87]; N=181)	# Trials (n)	Treatment Mean or % (n/N)	Control Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
I-PSS score, mean change from baseline	2 (181)	-2.2	-3.2	EQUIVALENTWMD = 0.96 [-0.49 to 2.40]	Insufficient (high study limitations, imprecise)
	1 (181)	-4	-5.4	Favors tamsulosin MD = 1.4 [CI NR]	Insufficient (high study limitations, imprecise)
I-PSS QoL, mean change from baseline	1 (40)	-1.6	-0.8	Favors sildenafil MD = -0.80 [-1.18 to -0.42]	Insufficient (high study limitations, unknown consistency)
Overall withdrawals	1 (41)	9.5 (2/21)	10 (2/20)	EQUIVALENTRR = 0.95 [0.15 to 6.13]	Insufficient (high study limitations,, unknown consistency, imprecise)
Withdrawals due to adverse effects	1 (41)	9.5 (2/21)	10 (2/20)	EQUIVALENTRR = 0.95 [0.15 to 6.13]	Insufficient (high study limitations, unknown consistency, imprecise)

CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; NS=no statistically significant difference; QoL=quality of life; RR=risk ratio; WMD=weighted mean difference

Efficacy of Vardenafil

One trial compared vardenafil 10 mg twice daily to placebo.[83] The 8-week trial randomized 222 participants with a mean age of 56 and a mean baseline I-PSS score of 17. Nearly all participants were white (99 percent). Approximately 60 percent of participants reported ED or ejaculatory problems. The trial was industry sponsored, conducted in Germany, and had low risk of bias.

Vardenafil improved mean I-PSS scores more than placebo (MD = -2.3; 95% CI: -3.64 to -0.9), suggesting that an appreciable number will benefit from vardenafil treatment. (insufficient evidence). Mean I-PSS scores decreased 5.9 with vardenafil and 3.6 with placebo, both exceeding MDD.

Study withdrawal for any reason was similar with vardenafil and placebo (insufficient evidence). Participants were more likely to withdraw due to adverse effects with vardenafil than placebo (low SoE). The proportion of patients with at least one adverse effect was higher with vardenafil than placebo (30 percent vs. 16 percent) (low SoE). Common adverse effects included headaches, flushing, and dyspepsia. Serious adverse effects were reported in two participants with vardenafil (myocardial infarction and hypertensive crisis) and three with placebo (hematochezia, meniscus injury, and knee surgery).

Efficacy of Vardenafil added to AB Monotherapy

One double-blinded trial (n=60) compared vardenafil 10 mg daily combined with tamsulosin 0.4 mg to tamsulosin monotherapy over 12 weeks.[76] Mean age of the participants was 67 and mean baseline I-PSS score was 19.6. The trial was conducted in Italy. No industry sponsorship was indicated and overall risk of bias was moderate.

Improvement in mean I-PSS scores was similar with combination and monotherapy (MD = -2.1; 95% CI: -4.8 to 0.6) (insufficient evidence). Mean reductions in I-PSS scores were 5.8 with combination and 3.7 with monotherapy, both achieving MDD.

One withdrawal was reported with tamsulosin. No participant withdrew due to adverse effects. Persistent adverse effects were reported in three participants with combination therapy

(headache with flushing, headache with stomach pain, stomach pain) and two with tamsulosin (headache, flushing). No serious adverse effects were reported.

Discussion

We conducted a systematic review with meta-analyses to assess the efficacy and comparative effectiveness of drugs recently proposed to treat LUTS/BPH including one new AB, several anticholinergics, one beta-3 agonist, and several PDE-5s. We sought to evaluate whether these drugs offered advantages over established treatments, primarily older ABs (i.e., tamsulosin, alfuzosin, doxazosin). Overall, we found that many of the new agents had a better efficacy in alleviating LUTS in men with BPH when compared to placebo, but offered no substantial benefit over more established agents. Some agents also raised increased safety concerns although the adverse effects were generally not severe and the event rate low. These new agents should therefore best be viewed as offering alternative treatment options of similar efficacy rather than superior management options. Consistent with AHRQ guidance on EPC reports, we did not include an economic analysis in this review to further the comparative effectiveness analysis with regards to resource utilization.

Using the established AHRQ strength of evidence rating system to describe our confidence in the estimates of effect, we were frequently forced to downgrade resulting in few “high” strength ratings. For the domain of study limitations/risk of bias, lack of blinding that raised the concern for performance and detection bias, was the most common reason for lowering our confidence in the estimates of effect. With regard to other domains that impact strength of evidence, lack of precision as judged with regards to width of the confidence interval of the pooled effect size estimate in relation to an MDD was a common issue that led to downgrading. The new AB, silodosin, was more effective for LUTS/BPH than placebo. However it was not more effective than the older AB, tamsulosin, and based on a direct head-to-head comparison, it was associated with an increased rate of adverse events.

Anticholinergics (including tolerodine and solifenacin) combined with established ABs improved LUTS/BPH more than placebo. While adverse effects were higher with the solifenacin/AB combination than with placebo (moderate SoE), evidence about adverse effects of tolterodine/AB combination compared with placebo was insufficient. Neither tolterodine nor solifenacin combined with AB was more effective than AB monotherapy, but both combination therapies were associated with higher adverse effects.

Another OAB drug, beta-3 agonist mirabegron, had also been tested in populations of men with LUTS/BPH. However, evidence was insufficient to draw conclusions about efficacy, comparative effectiveness, or adverse effects.

Tadalafil, the single FDA-approved PDE-5 for BPH, was more effective than placebo in treating LUTS/BPH. The associated averse effects were higher based (high SoE). However, efficacy of tadalafil was similar (alfuzosin) or inferior (tamsulosin) to AB monotherapy. Evidence was insufficient to assess efficacy and adverse effects of sildenafil and vardenafil. Combination therapy with tadalafil and AB was more effective than AB monotherapy in treating LUTS/BPH with a small effect size; however, strength of evidence was low. Most trials making this comparison were high risk of bias because they were open label or inadequately blinded. Results may apply only to select populations because most trials enrolled males who had not benefited from AB monotherapy, and most participants had ED history. One double-blind trial showed a statistically significant and meaningful difference between treatments.

Limitations

Our review sought to assess the short-, intermediate-, and long-term efficacy and comparative effectiveness of drugs newly used to treat LUTS/BPH. All RCTs were of short duration and therefore provided no data on intermediate- and long-term outcomes and adverse effects. In addition, we found no data on the impact of these agents on long-term disease progression and rates of treatment failure. Given that LUTS/BPH is a chronic and progressive condition, we can say little about treatments for the entire course of the disease.

In the body of evidence summarized in this report, AUR was a relatively rare adverse effects. However, not only did the available trials have a short durations but participants in trials of agents known to affect bladder contractility were sometimes excluded for pre-existing increased postvoid residuals, thereby possibly removing patients at greatest risk and lowering the incidence of AUR.

This review used pre-specified patient important outcomes that were believed to be most important to patients and critical to decision-making about treatment. The focus was summary measures such as IPSS that captured a number of individual symptoms. To the extent that patients or providers are interested in alleviating specific individual symptoms such as nocturia, this report does may not provide that information be helpful.

While the instrument most commonly used across trials, IPSS, has an anchor-based MDD, this was not used consistently in the original research to conduct responder analyses. Such an analysis pooled across studies would have provided the ideal efficacy outcome. Applying the MDD to weighted mean differences during systematic review is not as straightforward. Comparing differences between treatment groups differs from comparing individuals pre- and post-treatment, so applying the MDD this way was approached cautiously with appropriate guidance. We tried to report mean changes from baseline per group in order to provide context about which groups made improvements exceeding the MDD. We also reported the confidence intervals associated with the difference between treatments because means do not accurately describe the range of the effects in the study population and can be misleading, especially when distributions are not standard (i.e., bimodal). We used the established MDD in assessing the precision of estimates. While we believe this to be helpful, statements that “an appreciable number of patients” may or may not have noticed a difference in their symptoms is inherently vague and therefore of limited value. Lastly, there is controversy as to whether a “minimal noticeable’ difference is a sufficient standard for therapeutic efficacy or effectiveness and should be replaced with a - likely higher - standard of a “clinically meaningful” difference in the future.

Another significant limitation was the number of unblinded trials. These were most often PDE-5 trials that compared PDE-5/AB combination therapy to AB monotherapy. This is especially concerning because our primary efficacy outcomes are subjective; therefore, improvements in ED symptoms could influence perception and responses without meaningful improvements in LUTS/BPH symptoms. We did not examine correlations between LUTS outcomes and ED outcomes because extracting ED outcomes was beyond the scope of this review. It is unclear why investigators would choose unblinded designs for these comparisons, but strength of evidence suffered as a result.

There is growing interest in identifying which treatments for LUTS/BPH work best for which patients. However, we identified few trials that examined effects within our prespecified subgroup. Data on subgroups were scattered across comparisons and these data provide no actionable information.

Applicability

The body of evidence that we reviewed in this report is largely based on randomized clinical trials that enrolled patients that may different from the general population. Specifically, most men enrolled in these trials were age 50 – 70 years of age, thereby most notably excluding older men who may be at higher risk for drug-related adverse events. In trials of agents that are known to decrease bladder contractility such as anticholinergics, participants were often screened for increased postvoid residuals and sometimes excluded those above a certain threshold. The incidence of AUR in an unscreened population may therefore be higher.

PDE-5s have an established role in the treatment of ED which is a prevalent condition in aging men; potential benefits of the daily use of these agents of sexual domain-related quality of life were outside the scope of this review. At the same time, long-term use for durations that exceed the time-horizon of randomized controlled trials may also increase the of adverse events such as hypotensive episodes, drug interactions and myocardial infarction, thereby raising safety concerns. It is also important to note that the FDA-approved dose of tadalafil for LUTS is 5 mg, whereas doses of up to 20 mg are commonly used to treat ED. Many of the PDE-5 trials primarily enrolled males with ED symptoms, so it is not clear whether benefits would be applicable to the LUTS/BPH population without ED symptoms.

Future Research Needs

Additional research would add valuable information on the treatment of LUTS/BPH. Trials with longer duration with disease progression outcomes would provide a longer range view of the treatment of this condition as it progresses with age. Additionally, trials examining subgroups (i.e., BMI status, age, comorbid conditions) and how they respond to various treatments might provide important information useful for decision-making. While we found little benefit from the newer drugs, it is possible that they provide benefits to select groups of patients.

Future studies would benefit from consistently conducting and reporting responder analysis in addition to analysis of I-PSS scores. While providing complementary information, information from a responder analyses may provide data that is intuitively easier to understand, for example through NNT and NNH.

Given the lack of long-term data, future high quality observational studies that assess the impact of these agents on disease progression, risk of both disease-related complications and drug-related side-effects, as well as their role in preventing BPH complications (AUR) and delaying or preventing surgery would be of great value to decision-makers.

Conclusion

Silodosin, solifenacin, and tadalafil show short-term efficacy as monotherapy or when combined with established therapy in improving LUTS attributed to BPH. However, efficacy was often accompanied by increased adverse effects. The magnitude of improvement in LUTS for silodosin or tadalafil was similar to that of tamsulosin. The effect of tolterodine or solifenacin combined with established ABs was similar to that of the established AB. Data were not available to assess long-term maintenance, prevention of disease progression (including AUR or need for surgical intervention), and adverse effects.

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Abbreviations

AB	Alpha blocker
ARD	Absolute risk difference
AUA-SI	American Urological Association Symptom Index
AUR	Acute urinary retention
BII	BPH Impact Index
BOO	Bladder outlet obstruction
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
ED	Erectile dysfunction
I-PSS	International Prostate Symptom Score
LUTS	Lower urinary tract symptoms
MDD	Minimal detectable difference
NNH	Number needed to harm
NNT	Number needed to treat
OAB	Overactive bladder
PICOTS	Population, interventions, comparisons, outcomes, timing, and setting
PVR	Postvoid residual urine
QoL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
SMD	Standardized mean difference
WMD	Weighted mean difference