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Comparative Effectiveness Review
Number 178

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

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Comparative Effectiveness Review

Number 178

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2012-00161-I

Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:
Michelle Brasure, Ph.D., M.S.P.H., M.L.I.S.
Roderick MacDonald, M.S.
Philipp Dahm, M.D., M.H.Sc.
Carin M. Olson, M.D., M.S.
Victoria A. Nelson, M.Sc.
Howard A. Fink, M.D., M.P.H.
Michael Risk, M.D., Ph.D.
Bruce Rwabasonga, M.B.Ch.B., M.P.H., M.H.A.
Timothy J. Wilt, M.D., M.P.H.

AHRQ Publication No. 16-EHC024-EF
May 2016

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This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00161-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Suggested citation: Brasure M, MacDonald R, Dahm P, Olson CM, Nelson VA, Fink HA, Risk M, Rwabasonga B, Wilt TJ. Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Review. Comparative Effectiveness Review No. 178. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00161-I.) AHRQ Publication No. 16-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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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 email list to learn about new program products and opportunities for input.

If you have 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, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Sharon B. Arnold, Ph.D.
Acting Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Arlene S. Bierman M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Acknowledgments

We thank Marilyn Eells, Cheryl Cole-Hill, and Jeannine Ouellette for their editorial help bringing the report to completion. We thank Carla Foster and Abid Khan of the American Urologic Association for their contributions. We also thank Dr. Aysegul Gozu and Dr. Jonathan Treadwell for their helpful editorial comments.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

Andrew Avins, M.D., M.P.H.*
Division of Research
Northern California Kaiser Permanente
Oakland, CA

Harris Foster, Jr., M.D.
Department of Urology
Yale School of Medicine
New Haven, CT

Chester Bernell Good, M.D., M.P.H., FACP
School of Medicine
University of Pittsburgh
Pittsburgh, PA

Ziya Kirkali, M.D.*
Program Director
Division of Kidney, Urology and Hematology
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, MD

J. Kellogg Parsons, M.D., M.H.S.
Department of Urology
UCSD Comprehensive Cancer Center
La Jolla, CA

Justin Sherman, M.C.S., Pharm.D.*
School of Pharmacy
University of Mississippi
Jackson, MS

*Provided input on draft report.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Michael J. Barry, M.D.*
Department of Medicine
Harvard Medical School
Boston, MA

Robert R. Byrne, M.D.
Ellison, Walton and Byrne
Athens, GA

Harris Foster, Jr., M.D.
Department of Urology
Yale School of Medicine
New Haven, CT

Richard M. Hoffman, M.D., M.P.H.
Professor of Internal Medicine and Epidemiology
Director, Division of General Internal Medicine
University of Iowa Carver College of Medicine/Iowa City VA Medical Center
Iowa City, IA

John M. Hollingsworth, M.D., M.S.*
Department of Urology
University of Michigan Medical School
Ann Arbor, MI

Ziya Kirkali, M.D.*
Program Director
Division of Kidney, Urology and Hematology
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, MD

Michael LeFevre, M.D., M.S.P.H.
Professor, Future of Family Medicine
University of Missouri Family and Community Medicine
Columbia, MO

Kevin T. McVary, M.D.*
Division of Urology
Southern Illinois University School of Medicine
Springfield, IL

Justin Sherman, M.C.S., Pharm.D.*
School of Pharmacy
University of Mississippi
Jackson, MS

*Provided input on draft report.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Mary Ann Forciea, M.D.
Medical Center
University of Pennsylvania
Philadelphia, PA

Angela B. Smith, M.D., M.S.
Department of Urology
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, NC

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

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and adverse effects of newer drugs to treat lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia (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 through July 2015. Two investigators screened titles and abstracts of search results and full text of relevant references for eligibility. Eligible studies evaluated efficacy and/or harms of one alpha blocker (AB) (silodosin), several antimuscarinics (tolterodine, solifenacin, fesoterodine), one beta-3 adrenoceptor agonist (mirabegron), and several phosphodiesterase type 5 (PDE-5) inhibitors (tadalafil, sildenafil) or combination therapy with one of these medications. They included randomized controlled trials (RCTs) with duration of at least1 month and observational studies for long-term (≥1 year) adverse events. We assessed risk of bias for RCTs, extracted data, pooled data for analysis when appropriate and feasible, and evaluated strength of evidence for comparisons on an outcome-specific basis.

Results. We synthesized evidence from 57 unique RCTs and 5 observational studies. Trials were generally short term (e.g., 12 weeks). Silodosin was more effective than placebo in improving LUTS but was similar to tamsulosin and had more adverse effects, including abnormal ejaculation. Solifenacin/AB combination therapy was better than placebo, but tolterodine/AB, solifenacin/AB, and fesoterodine/AB combination therapy were similar to AB monotherapy, and combination therapy often had more adverse effects. Tadalafil improved LUTS more than placebo but had more adverse effects. Tadalafil and tamsulosin were similar in improving LUTS. We identified trials testing other drugs (mirabegron, oxybutynin, darifenacin, sildenafil, and vardenafil) but found the evidence insufficient to draw conclusions about efficacy, comparative effectiveness, or adverse effects. Evidence was insufficient to assess long-term efficacy, prevention of symptom progression (e.g., acute urinary retention or need for surgical intervention), or adverse effects.

Conclusions. Several drugs newly used for LUTS attributed to BPH, alone or in combination with older AB, showed evidence of efficacy in short-term studies; however, comparative effectiveness for silodosin, fesoterodine/AB combination, and tadalafil showed that outcomes were similar to older AB monotherapy and adverse effects were often higher with the newly used drugs or combination therapies. Evidence on long-term efficacy and adverse effects was insufficient.

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Introduction

Background

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 histologic BPH.[2]

About half of men with BPH develop an enlarged prostate gland, called benign prostatic enlargement (BPE); among these, about half develop some degree of bladder outlet obstruction (BOO).[3] BOO and/or changes in smooth muscle tone and resistance that can accompany BPH may 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 urinary stream, straining to void, 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] LUTS attributed to BPH may 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. However, an enlarged prostate may not cause any urinary symptoms, so when LUTS are 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 attributed to BPH.[5] Treatment decisions can typically be based on symptoms and degree of bother without need to perform specialized tests such as uroflowmetry and postvoid residual urine (PVR) measurement.[1,3]

Lifestyle interventions such as modifying fluid intake or toileting behavior are typically the first-line treatments to reduce symptoms in patients with LUTS/BPH. When necessary, pharmacological treatment also may be initiated to reduce symptoms and prevent or delay disease progression. Pharmacological management of LUTS attributed to BPH has evolved over the last 25 years. Table 1 provides a list of drugs commonly used to treat LUTS attributed to BPH. Alpha blockers (ABs) and 5-alpha reductase inhibitors (5-ARIs) have been used to treat LUTS attributed to BPH for decades and their efficacy has been established. Recently, newer drugs in these classes and drugs in other classes approved for other indications have shown promise in treating LUTS attributed to 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 LUTS attributed to BPH.[7] These anticholinergic drugs work directly on the bladder smooth muscle as opposed to ABs and 5-ARIs, which target the prostate.

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 attributed to BPH, and this usage may increase in the future.[8]

Tadalafil, a phosphodiesterase type 5 inhibitor (PDE-5), was approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction (ED) in 2003 and for the treatment of BPH in 2011. Other PDE-5 inhibitors have been used off-label for LUTS attributed to BPH, both alone and in combination with ABs.

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Based on the wide variety of medications available to treat LUTS attributed to BPH, it is possible that tailoring treatment with single medications or medication combinations can maximize efficacy or effectiveness and minimize adverse effects. Some patients are more bothered by specific symptoms that may be preferentially improved by certain medications. Men with LUTS attributed to BPH often have other health conditions or are taking other medications that should be considered in choice of pharmacologic therapy for LUTS attributed to BPH.

The primary goals of LUTS attributed to 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] These two instruments are identical with the exception of an additional question in the I-PSS regarding global bother.

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, are not relevant to primary care settings, and it is unclear whether they should guide treatment decisions.

Clinical practice guidelines play an important role in guiding evidence-based clinical practice. According to Institute of Medicine standards, they need to be based on high quality systematic reviews of the entire body of evidence and there is an important need to provide an up-to-date systematic review that accounts for more recently approved medications for LUTS attributed to BPH. Our review comprehensively assesses medications for LUTS attributed to 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 attributed to BPH (Table 1).

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

Key Questions (KQs)

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

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

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

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Table 1. Medications used to treat LUTS attributed to BPH

Drug Class - Mechanism of Action (FDA)	Medication
Alpha 1 blockers (ABs): Inhibit smooth muscle contraction by blocking alpha-1 receptors and decreasing resistance to urinary flow.	**Silodosin[a] [Rapaflo]**
	Terazosin[a] [Hytrin] Alfuzosin[a] [Uroxatral] Doxazosin[a] [Cardura] Tamsulosin[a] [Flomax]
5 alpha reductase inhibitors (5-ARIs): Inhibit 5-alpha reductase, an isoenzyme metabolizing testosterone to DHT, blocking conversion of testosterone to DHT and reducing DHT.	Finasteride[a] [Proscar]
	Dutasteride[a] [Avodart]
Anticholinergic agent: Relaxes smooth muscle in urinary bladder.	**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 smooth muscle of the bladder.	**Mirabegron[b] [Myrbetriq]**
Phospodiesterase type 5 (PDE-5) inhibitors: Exact mechanism unclear, presumed to selectively inhibit PDE-5, increasing cyclic guanosine monophosphate (cGMP) and causes smooth muscle relaxation.	**Tadalafil[a, d] [Cialis]** **Sildenafil[c] [Viagra]** **Avanafil[d] [Stendra]** **Vardenafil[d] [Staxyn, Levitra]**

BPH=benign prostatic hyperplasia; cGMP=cyclic guanosine monophosphate; DHT= dihydrotestosterone; FDA=Food and Drug Administration, LUTS=lower urinary tract symptoms; [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.

Source: Micromedex[9]

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	Medications recently FDA approved for BPH or newly studied off-label for LUTS attributable to BPH
Comparators	Placebo or "older" LUTS attributed to BPH medication (i.e., previously FDA approved for BPH) (Table 1).
Outcomes	Primary Outcomes: LUTS scores (I-PSS, AUA-SS); 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, 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.

AUA-SI=American Urological Association Symptom score; AUR=Acute urinary retention; BII-BPH Impact Index; BMI=Body mass index; BPH=Benign prostatic hyperplasia; FDA=Food and Drug Administration; I-PSS=International Prostate Symptom Scale; LUTS=Lower urinary tract symptoms

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Methods

We developed an a priori analytical framework to guide the systematic review process (Appendix A). We systematically searched 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 defined these newer drugs as those that have been FDA approved for BPH since 2008 or which have been studied for treatment of BPH are not currently FDA approved for this indication. 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 natural language terms for each included drug class and drug with filters for study design (Appendix B) to identify relevant RCTs through July 2015. We additionally searched for large ($n \geq 100$), longer-term (≥ 1 year duration) 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 by two investigators to determine if inclusion criteria were met. We included trials published in English that studied the PICOTS described above. Inclusion criteria did not restrict RCTs by minimal sample size. Differences in screening decisions were uncommon and resolved by consultation between investigators. If necessary, consultation with a third investigator was used to make the final decision. We searched ClinicalTrials.gov and the Food and Drug Administration Web site to identify additional completed and ongoing studies for inclusion and assessment of reporting 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. Postcrossover data were not used. Risk of bias of eligible studies were assessed using AHRQ guidance by one investigator and reviewed by a second.[10] Relevant components included participant selection, method of randomization, allocation concealment, blinding, completeness of followup (attrition), and appropriateness of analytic methods. Investigators conferred with each other 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 were believable given the study's limitations.

We assessed clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[11] When three or more trials reported similar comparisons and outcomes, data were pooled using a Hartung, Knapp, Sidik, and Jonkman (HKSJ) method[12] random effects model for I-PSS responders or mean changes in I-PSS scores in Stata.[13] We pooled other outcomes in RevMan[14] and converted DerSimonian-Laird random effects confidence intervals to HKSJ confidence intervals using an excel spreadsheet provided in Inthout et al.[12] Risk ratios (RR) with corresponding 95 percent confidence intervals (CI) were estimated for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs were estimated for continuous outcomes. We assessed between study variance with Tau^2 and measured the magnitude of heterogeneity with the I^2 statistic. 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.[11,15]

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We interpreted efficacy and comparative effectiveness using established thresholds indicating clinical significance. Table 3 provides a list of these instruments, basic characteristics, and relevant thresholds for classifying improvement.[16] Barry et al. conducted an anchor-based study to identify the minimal detectable difference (MDD) in I-PSS and BPH Impact Index (BII) scales.

When the established MDD or other valid threshold was used in the original research to classify individuals as responders and nonresponders, we pooled those results. When mean scale scores or mean change in scale scores for instruments with established MDDs, we used the MDD to interpret the WMD. Johnson et al. suggest an interpretation of the differences between groups in relation to the established minimal important difference.[17] This approach suggests that when the WMD is equal to or larger than the MDD, many patients may have gained detectable benefits from treatment; when the WMD is at least half of the MDD but less than the MDD, an appreciable number of participants have likely achieved a clinically meaningful improvement; and when the WMD is less than one-half of the MDD, it is unlikely that an appreciable number of participants achieve detectable benefits. Following this guidance, we concluded that statistically significant differences were clinically meaningful when the WMD was at least 50 percent of the MDD. Therefore, the statistically significant WMD between treatment groups for post-treatment or change in I-PSS must be equal to or greater than -1.5 and the WMD between treatment groups for post-treatment or change in BII must be equal to or greater than -0.25. No threshold was established for the I-PSS QoL (quality of life) question. Responses to this question are ordinal and range from 0 to 6. We used an MDD of 1 to assess efficacy and comparative effectiveness. Therefore, if this question was analyzed as a continuous variable, we required statistical significance and a WMD of at least 0.5 to conclude a clinically meaningful difference.

The overall strength of evidence (SoE) for primary outcomes of KQ1 within each comparison was evaluated based on the number and size of trials, point estimate(s), relative difference or equivalence of the comparison-outcome, placement of the CI, and the assessed SoE domains (five required domains and three optional domains). The five required domains include: (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.[18] Optional domains of dose-response association, plausible confounding that would increase the observed effect, and strength of association were assessed to potentially upgrade strength of evidence assessments based upon required domains.[18] Based on these elements, we assessed the overall SoE for each comparison and outcome as:

- **High:** We are very confident that estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not likely change the conclusion.
- **Moderate:** We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- **Low:** We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- **Insufficient:** We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion."[18]

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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.[19]

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

Instrument	Range (Points)	Scoring	Thresholds Indicating Different Levels of Improvement**[16]
International ProstateSymptom Score (I-PSS)**	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.

** Also known as the American Urological Association symptom score

BPH=benign prostatic hyperplasia BPH-LUTS=benign prostatic hyperplasia-lower urinary tract symptoms; LUTS=lower urinary tract symptoms MDD=minimal detectable difference; QoL=Quality of life

** Based on a baseline I-PSS of approximately 16.

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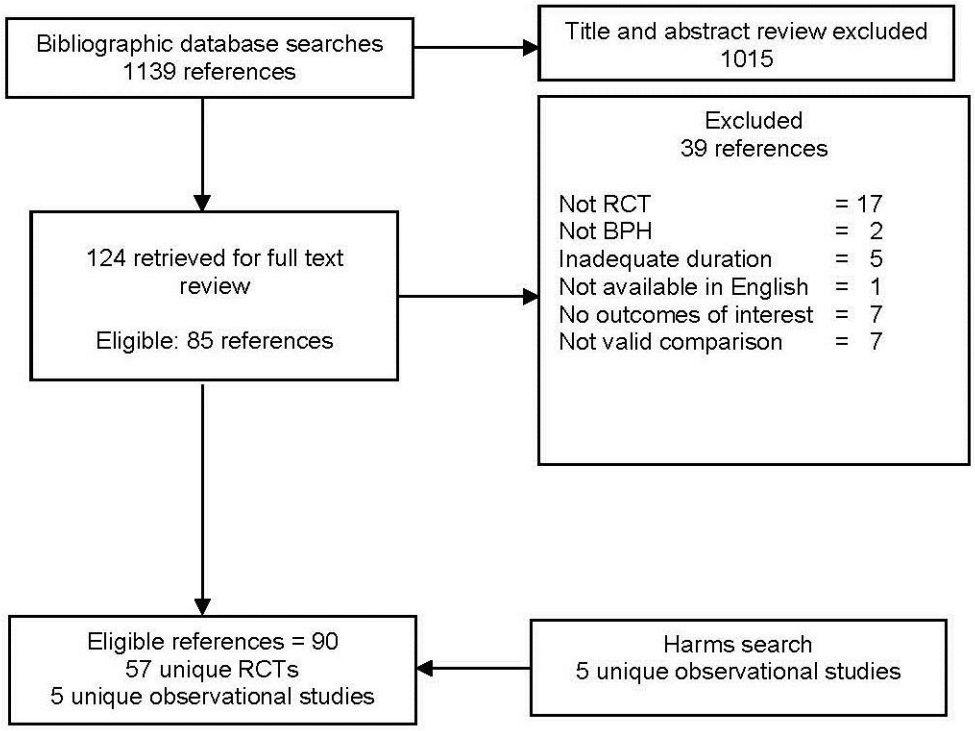
Results

Search Results

Our search identified 1139 citations, of which 124 required full text review after title and abstract screening, and 85 met eligibility criteria for inclusion in this review (Figure 1). These 85 records reported results from 57 unique RCTs. Of the articles we identified and determined to be eligible, silodosin was studied in 11 trials (reported in 19 articles);[20-38] anticholinergics were studied in 20 trials (reported in 24 articles);[39-63] beta-3 agonists were studied in 2 trials (reported in 2 articles);[64,65] and PDE-5 inhibitors were studied in 24 trials (reported in 39 articles).[66-104] We screened the full text of 15 references identified as potentially relevant to address long-term harms. Five met our inclusion criteria.[77,105-108]

Figure 1. Literature flow diagram



BPH=benign prostatic hyperplasia; RCT=randomized controlled trial.

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 KQs are discussed within each drug-specific section.

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Alpha Blockers

Supporting tables and figures relevant to new ABs appear in Appendix D. In all trials, men had to meet a minimum IPSS score at baseline, typically 8 or greater or 13 or greater. Some trials required men to have a Qmax (peak flow rate) of less than 15 mL/second at baseline.

Key Points

- Silodosin improved short-term LUTS more than placebo; effect size was small (moderate to high SoE). Adverse effects, most commonly abnormal ejaculation, were higher with silodosin than placebo (high SoE).
- Silodosin and tamsulosin were similarly effective in improving short-term LUTS (moderate SoE), though withdrawals due to adverse effects were higher with silodosin (moderate SoE).

Silodosin Versus Placebo

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 12-weeks (Table 4).[28,30,31] Mean age of participants was 63 and mean baseline I-PSS score was 20 (range 17 to 21). In the two trials that reported race/ethnicity, nearly all participants were white (93%).[28,30] Two trials were conducted in the United States,[30] one in Europe,[28] and one in Japan.[31] Three trials reported industry sponsorship[28,30] and one did not report sponsorship.[31] Overall risk of bias was low in three trials[28,30] and was moderate in one trial.[31]

Silodosin improved LUTS attributed to BPH more than placebo (high to moderate SoE). Two trials conducted a responder analysis, defined as $\geq$25 percent reduction in baseline I-PSS score.[28,31] The proportion of responders was higher with silodosin (66% and 76%) than placebo (51% in both trials, RR 1.38) (high SoE). The absolute risk differences were 16 and 25 percent. Mean change in I-PSS scores also was larger with silodosin than placebo (WMD = -2.7). 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. Two trials reported the I-PSS QoL index as a categorical outcome.[28,34] Improvement in the I-PSS QoL favored silodosin, with 32 and 43 percent reporting being "delighted, pleased, or mostly satisfied" compared with 23 and 33 percent with placebo (high SoE). One trial assessed I-PSS QoL based on mean change from baseline and showed greater improvement with silodosin than placebo (MD = -0.60).[31] None of the trials reported disease progression or treatment failure outcomes.

Study withdrawal for any reason was similar with silodosin or placebo (insufficient SoE).[28,30] 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%; RR 1.38) (high SoE). The most common adverse effect with silodosin was abnormal ejaculation. We found limited information on serious adverse events. Marks et al. reported that serious adverse effects were infrequent and similar with silodosin and placebo, approximately one and two percent respectively.[30] 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.[28]

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Table 4. Evidence overview: silodosin versus placebo

Silodosin 8 mg vs. Placebo *(4 RCT[28,30,31] N=1759)*	# Trials (n)	Silodosin Mean or % (n/N)	Placebo Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Responders (> 25% reduction in I-PSS scores) Chapple, 2011[28] Kawabe, 2006[31]	Chapple, 2011 (566) Kawabe, 2006 (263)	Chapple, 2011 66 (248/371) Kawabe, 2006 76 (133/174)	Chapple, 2011 51 (94/185) Kawabe, 2006 51 (45/89)	Favors silodosin Chapple, 2011 RR = 1.32 [1.12 to 1.54] Kawabe, 2006 RR = 1.51 [1.21 to 1.89]	High
I-PSS score, *mean change from baseline* Chapple, 2011[28] Marks, 2009[30] Kawabe, 2006[31]	3 (1743)	-6.9	-4	Favors silodosin WMD = -2.68 [-3.91 to -1.44]	Moderate (imprecise)
I-PSS QoL, reporting "delighted, pleased, or mostly satisfied" Marks, 2009[30] Chapple, 2011[28]	2 (1494)	Chapple, 2011 43 (163/381) Marks, 2009 32 (149/466)	Chapple, 2011 33 (63/190) Marks, 2009 23 (103/457)	Favors silodosin Marks, 2009 RR = 1.42 [1.14 to 1.76] Chapple, 2011 RR = 1.29 [1.02 to 1.63]	High
I-PSS QoL, *mean change from baseline* Kawabe, 2006[31]	1 (264)	-1.7	-1.1	Favors silodosin MD = -0.60 [-0.92 to -0.28]	Moderate (imprecise)
Overall withdrawals Marks, 2009[30] Chapple, 2011[28]	2 (1494)	Marks, 2009 11 (53/466) Chapple, 2011 7 (25/381)	Marks, 2009 8 (38/457) Chapple, 2011 9 (18/190)	Marks, 2009 RR = 1.37 [0.92 to 2.03] Chapple, 2011 RR = 0.69 [0.39 to 1.24]	Insufficient (imprecise, CI not centered around 0)
Withdrawals due to adverse effects Marks, 2009[30] Chapple, 2011[28] Kawabe, 2006[31]	3 (1759)	5 (56/1023)	2 (17/736)	Greater with silodosin RR = 2.41 [1.01 to 5.76]	High
Participants with ≥1 adverse effect[28,30,31]	3 (1757)	53 (545/1022)	38 (277/735)	Greater with silodosin RR = 1.38 [1.05 to 1.81]	High

CI=confidence intervals; I-PSS=International Prostate Symptom Score; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; MD=mean difference; WMD=weighted mean difference

Long-Term Adverse Events

We identified two observational studies reporting longer term adverse effects related to silodosin treatment.[106,108] These studies were observational and therefore have limited internal validity. We did not assess strength of evidence for long-term adverse events but provide the information descriptively because it represents the best available evidence. Adverse events described in the one trial reporting data were similar to those identified in silodosin RCTs.

Marks et al. analyzed adverse effects in a 40-week open label extension of a previous RCT (cumulative treatment duration of 52 weeks).[108] 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 events. Twenty-nine patients (4.4%) experienced serious adverse events including two deaths; none of the serious adverse events, including the deaths, were considered drug-related by the researchers. Criteria for determining whether serious adverse events were drug-related were not

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described in the report. The most common adverse events were retrograde ejaculation (21%), diarrhea (4%), and nasopharyngitis (4%).

Yoshimura et al. reviewed FDA data for adverse effects associated with ABs and found the data on silodosin insufficient to compare with other ABs.[106]

Efficacy and Patient Demographic and Clinical Characteristics

We identified two posthoc analyses that evaluated the effect of our prespecified patient demographic or clinical characteristics on the efficacy of silodosin.[31,32] Novara et al. pooled data (n=1484) from two previous RCTs[28,30] to examine the effect of age, BMI, and baseline LUTS severity on response to treatment using linear regression models.[32] 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.[31]

Dosing of Silodosin

We identified two noninferiority trials comparing different silodosin doses.[20,23] Choo et al. compared silodosin 4 mg taken twice daily with 8 mg taken once daily for 12-weeks in a population of Korean men with LUTS (n=532).[23] Mean age was 64 and mean baseline I-PSS score was 19. Risk of bias was moderate. They found no differences in any outcome or adverse effect.

Seki et al. compared silodosin 4 mg taken once daily with 4 mg taken twice daily for 12-weeks in a population of older Japanese men with LUTS and OAB symptoms (n=268).[20] Mean age was 72 and mean baseline I-PSS score was 20. The trial was open-label and risk of bias was high. They found no differences in mean changes in I-PSS scores or adverse effects.

Silodosin Versus Tamsulosin

The only comparative effectiveness trials we identified compared silodosin with tamsulosin. Eight trials randomized males with LUTS attributed to BPH (n=1705) to silodosin 8 mg daily versus tamsulosin 0.2 to 0.4 mg daily. All trials lasted 4- to 12-weeks (Table 5).[22,24-29,31] Mean age of the participants was 67 years and mean I-PSS score at baseline was 18 (range 17 to 20) in silodosin and tamsulosin arms. Six trials conducted in Asia used a 0.2 mg dose of tamsulosin, a dose lower than the generally recommended 0.4 mg dose utilized in the United States and Europe[22,24-27,31] Two trials conducted in Europe or India used a 0.4 mg dose of tamsulosin.[22,28] Only the European trial reported race/ethnicity, and all its participants were white.[28] Three trials were crossover studies (4 week phases each) and only data from the first-phases of these trials were used in the analyses.[24,27,29] Two trials reported industry sponsorship.[25,28] Overall risk of bias was low in two trials,[22,28] moderate in four trials,[24-26,31] and high in two trials.[27,29]

Three trials conducted responder analysis (defined as >25 percent reduction in I-PSS score).[26,28,31] 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 I-PSS scores similar to enrollees. Silodosin and tamsulosin were similar in improving mean I-PSS scores (moderate SoE). Mean reductions in I-PSS scores were 7.8 and 7.2 points with silodosin and tamsulosin when we pooled trials using either dose of tamsulosin. Results were similar in trials using tamsulosin 0.4 mg. Both treatments reduced mean I-PSS scores by more than the MDD of three points. Overall improvement in the I-PSS QoL also was similar with silodosin and tamsulosin, but heterogeneity

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between studies was substantial (I^2 = 76%), thereby reducing our confidence (moderate 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 effect 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. Trials reported that withdrawals due to adverse effects were only observed with silodosin[24,27] and that abnormal ejaculation was the most common.[24,27,29] 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.[28]

Table 5. Evidence overview: silodosin versus tamsulosin

Silodosin 8 mg vs. Tamsulosin 0.2 to 0.4 mg ***(8 RCT;*** [22,24-29,31] ***N=1705)***	**# Trials (n)**	**Silodosin Mean or % (n/N)**	**Tamsulosin 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 (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)[25,28,31]	3 (1283)	72 (456/632)	68 (440/651)	SIMILAR RR = 1.07 [0.91 to 1.26]	Moderate (moderate study limitations, upgrade for plausible confounding)
Responders, based on ≥25% reduction in total I-PSS score (Silodosin 8 mg vs. Tamsulosin 0.2 mg) Yu 2011[25] Kawabe, 2006[31]	2 (536)	Yu, 2011 86 (75/87) Kawabe, 2006 76 (133/174)	Yu, 2011 82 (68/83) Kawabe, 2006 66 (126/192)	Yu, 2011 RR = 1.05 [0.92 to 1.20] Kawabe, 2006 RR = 1.16 [1.02 to 1.33]	Insufficient (moderate study limitations, inconsistent, imprecise)
Responders, based on ≥25% reduction in total I-PSS score (Silodosin 8 mg vs. Tamsulosin 0.4 mg) Chapple, 2011 [28]	1 (747)	66 (248/371)	65 (246/376)	SIMILAR RR = 1.02 [0.92 to 1.13]	Low (moderate study limitations, unknown consistency)
I-PSS score, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	7 (1538)	-7.8	-7.2	SIMILAR WMD = -0.63 [-1.62 to 0.36]	Moderate (moderate study limitations)
I-PSS score, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.2 mg)	5 (738)	-8.3	-7.4	SIMILAR WMD = -0.69 [-3.00 to 1.66]	Moderate (moderate study limitations, imprecise, upgrade for plausible confounding)
I-PSS score, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	Pande, 2014 (53) Chapple, 2011 (747)	Pande, 2014 -11.7 Chapple, 2011 -7.0	Pande, 2014 -11.0 -6.7 Chapple, 2011 -4.7	SIMILAR Pande, 2014 MD = -0.70 [-2.42 to 1.02] Chapple, 2011 MD = -0.30 [-1.03 to 0.43]	Moderate (moderate study limitations)
I-PSS QoL, reporting "delighted, pleased, or mostly satisfied'	1 (765)	Chapple, 2011 44%	Chapple, 2011 45%	SIMILAR RR 0.98 [0.83 to 1.15]	Low (unknown consistency)

Silodosin 8 mg vs. Tamsulosin 0.2 to 0.4 mg ***(8 RCT;*** [22,24-29,31] ***N=1705)***	**# Trials (n)**	**Silodosin Mean or % (n/N)**	**Tamsulosin Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS QoL, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.2 mg)	5 (728)	-1.5	-1.3	SIMILAR WMD = -0.16 [-0.80 to 0.48]	Moderate (moderate study limitations, inconsistent, upgrade for plausible confounding)
I-PSS QoL, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	1 (747)	-1.3	-1.2	SIMILAR Chapple, 2011 MD = -0.30 [-1.03 to 0.43]	Low (imprecise, unknown consistency)
Overall withdrawals (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	4 (1125)	9 (53/563)	9 (49/562)	SIMILAR RR = 1.05 [0.73 to 1.5]	Low (study limitations, imprecise)
Overall withdrawals (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	Pande, 2014 (53) Chapple, 2011 (747)	Pande, 2014 19 (6/32) Chapple, 2011 7 (25/381)	Pande, 2014 7 (2/29) Chapple, 2011 5 (20/384)	Pande, 2014 RR = 2.72 [0.60 to 12.42] Chapple, 2011 RR = 1.26 [0.71 to 2.23]	Insufficient (moderate study limitations, imprecise)
Withdrawals due to adverse effects (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	3 (1222)	5 (30/601)	3 (16/621)	Greater with silodosin RR = 1.96 [1.04 to 3.71]	Moderate (moderate study limitations, upgrade for plausible confounding)
Withdrawals due to adverse effects (Silodosin 8 mg vs. Tamsulosin 0.4 mg) Chapple, 2011[28]	1 (747)	2 (8/381)	1 (4/384)	RR = 2.02 [0.61 to 6.64]	Insufficient (moderate study limitations, imprecise)
Participants with ≥1 adverse effect (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	3 (1338)	52 (342/659)	46 (314/679)	RR = 1.11 [0.95 to 1.29]	Insufficient (moderate study limitations, imprecise)
Participants with ≥1 adverse effect (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	1 (747)	35 (133/381)	29 (111/384)	RR = 1.21 [0.98 to 1.49]	Insufficient (imprecise, unknown consistency)

CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; QoL=quality of life; RCT=randomized controlled trial; 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. To be enrolled in the anticholinergic trials men had have symptomatic BPH (typically meeting a minimum IPSS score at baseline, usually 12 or greater) and have OAB symptoms such as having 8 or more micturitions over 24 hours and having urgency episodes. Several trials excluded men with post

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void residual volumes greater than 100-250 mL. Some trials required a Qmax (peak flow rate) of 15 mL/second or less (some requiring a minimum of 4 or 5 mL) at baseline.

Key Points

- Tolterodine/AB combination and AB monotherapy were similarly effective for short-term LUTS (moderate SoE). Evidence was insufficient to conclude whether adverse effects were different between treatments.
- Solifenacin/AB combination therapy improved short-term LUTS more than placebo over the short term, though effect size was small (moderate SoE). Evidence was insufficient to conclude whether adverse effects were different between treatments.
- Solifenacin/AB combination and AB monotherapy were similarly effective for short-term LUTS (moderate SoE). Having more than one adverse effect was more common with solifenacin/AB combination therapy than with AB monotherapy (moderate SoE).

Tolterodine

Tolterodine Versus Placebo

One 12-week trial compared tolterodine 4 mg daily (n=217) with placebo (n=222) in men with LUTS and OAB symptoms. Individuals with a baseline postvoid residual of >200 ml were excluded. Mean age was 62 and mean baseline I-PSS score was 20.[58] OAB symptoms were evaluated using bladder diaries. Most participants were white (81%). The trial was conducted in the United States and was industry-sponsored. Overall risk of bias was low.

Changes in I-PSS score and I-PSS QoL were similar with tolterodine and placebo (low SoE). Urinary retention was reported in two participants with tolterodine and three participants with placebo.

There was insufficient SoE for overall withdrawals and withdrawal due to adverse effects. Dry mouth was reported more frequently with tolterodine than placebo (7% vs. 2%).

Tolterodine/AB Combination Versus Placebo

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.[58] Individuals with baseline postvoid residual >200 ml were excluded. Mean age was 61 and mean baseline I-PSS was 20. The trial was conducted in the United States and was industry-sponsored. Risk of bias was low.

Combination therapy improved mean change in I-PSS (MD = -1.80) and I-PSS QoL more than placebo (low SoE).

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

Tolterodine/AB Combination Versus AB Monotherapy

Four trials randomized males with LUTS and OAB symptoms (n=1249) to a combination of tolterodine 4 mg plus AB versus AB monotherapy with tamsulosin, doxazosin, or alfuzosin (Table 6).[41,52,56,58] OAB symptoms were generally evaluated using bladder diaries. Mean age was 63 and mean baseline I-PSS score was 20 (range = 19 to 24). One study was a multicenter study from several countries (Europe, North America, Asia, and South Africa),[56] and one was a multicenter study performed in the United States;[58] the others were conducted in South Korea[52]

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and Pakistan,[41] All but one study reported industry sponsorship. Overall risk of bias for three trials was low and one trial had high risk of bias.[41]

Only the one high risk of bias trial[41] conducted a responder analysis, defined as a 3-point improvement in I-PSS score from baseline. Although the proportion of responders was greater in the combination group than the AB monotherapy group (77% vs. 29%), SoE was insufficient. Pooled results from all trials found mean changes in I-PSS scores were similar with combination and monotherapy (WMD = -0.19) (moderate SoE). Pooled results from three studies showed mean change in I-PSS QoL was similar between combination and monotherapy (low SoE).[52,56,58]

There were six incidences of acute urinary retention (AUR) in the combination group and two in the monotherapy group (insufficient evidence).[52,56,58] No other indicators of disease progression/treatment failure were reported. Withdrawal for any reason or due to adverse effects was similar with combination and monotherapy (low SoE). The proportion reporting one or more adverse effect was similar with combination and monotherapy in the one trial reporting this outcome (insufficient SoE).[56]

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

Tolterodine, 4 mg Plus AB vs. AB ***(4 RCT[41,52,56,58] N=1297)***	**# Trials (n)**	**Tolterodine/ AB Combo Mean or % (n/N)**	**AB Mono Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
Responders (3-point improvement in I-PSS score from baseline)	1 (70)	77 (27/35)	29 (10/35)	Favors Combination RR = 2.7 [1.55 to 4.70]	Insufficient (high study imitations, unknown consistency)
I-PSS score, *mean change from baseline*	4 (1249)	-5.9	-5.6	SIMILAR WMD = -0.19 [-1.08 to 0.69]	Moderate (low to moderate study limitations)
I-PSS QoL, *mean change from baseline*	3 (1182)	-1.3	-1.1	SIMILAR WMD = -0.34 [-1.14 to 0.46]	Low (imprecise, inconsistent)
Acute urinary retention	3 (1268)	1 (6/639)	0 (2/629)	OR = 2.69 [0.25 to 28.96]	Insufficient (indirect, very imprecise)
Overall withdrawals	3 (1268)	16 (101/639)	14 (88/629)	SIMILAR RR = 1.11 [0.53 to 2.34]	Low (imprecise, CI not centered around 0)
Withdrawals due to adverse effects	3 (1268)	6 (36/639)	3 (16/629)	RR = 2.17 [0.93 to 5.06]	Insufficient (imprecise, CI skewed towards difference, but not statistically significant)
Participants with ≥1 adverse effect	1 (652)	35 (114/329)	28 (89/323)	RR = 1.26 [1.00 to 1.58]	Insufficient (imprecise, unknown consistency)

AB=alpha-blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; OR-odds ratio; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Efficacy and Patient Demographic and Clinical Characteristics

We identified one small 12-week trial (n=70) with a high risk of bias that evaluated the adjunctive efficacy of tolterodine added to alfuzosin versus alfuzosin monotherapy by age.[41] Combination therapy improved symptoms more than monotherapy in men between 51 and 70, but not in those 50 and younger or over 70.

Tolterodine/AB or 5-ARI Combination Versus AB or 5-ARI 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 (5-ARI) (n=50) versus doxazosin and/or dutasteride monotherapy (n=87) in men with LUTS and storage symptoms.[54] Individuals with a baseline postvoid residual of >250 ml were excluded. The men were older, with a mean age of 76, and mean

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baseline I-PSS score was 18. The trial was conducted in Taiwan. Industry-sponsorship was not reported. Overall risk of bias was high.

Mean change in I-PSS score for the tolterodine plus doxazosin/dutasteride combined group was -8.9 points and -6.5 points for the doxazosin/dutasteride group (insufficient SoE).

Acute urinary retention requiring catheterization was reported for two participants (4%) in the tolterodine plus doxazosin/dutasteride combined group and three (3.5%) in 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% vs. 6%), leading to study withdrawal of six combination participants. However, SoE was insufficient for all efficacy and harms outcomes.

Tolterodine Versus AB

Two 12-week trials compared tolterodine with AB monotherapy.[40,58] Data were not pooled due to the heterogeneity in study populations in terms of LUTS severity.

One trial compared tolterodine 4 mg (n=217) with tamsulosin 0.4 mg (n=222).[58] Mean age was 62 and mean baseline I-PSS was 20. The trial was conducted in the United States and was industry-sponsored. Overall risk of bias was low.

Mean changes in I-PSS (MD = 0.90) and I-PSS QoL (MD = -0.10) were similar with tolterodine and tamsulosin groups (low SoE). Three cases of acute urinary retention were reported with tolterodine compared to none with tamsulosin. Overall withdrawals and withdrawal due to adverse effects were similar with tolterodine and tamsulosin (insufficient SoE). Dizziness was reported more frequently with tamsulosin than tolterodine (6% vs. 1%).

One trial compared tolterodine 4 mg (n=108) with doxazosin 4 mg daily (n=94) in participants with predominant storage LUTS.[40] Those with baseline postvoid residual >250 ml were excluded. Mean age was 69 and mean baseline I-PSS was 11.5, substantially lower than the previous trial. The trial was conducted in Taiwan. Industry sponsorship was not reported. No blinding was reported and overall risk of bias was high.

Mean changes in I-PSS (MD = -0.20) and I-PSS QoL (MD = -0.20) 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 doxazossin (insufficient evidence).

Solifenacin

Solifenacin Versus Placebo

One 12-week 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.[44] Individuals with a baseline postvoid residual of >200 ml were excluded. Mean age was 65 and mean baseline I-PSS score was 19. Nearly all men were white. The trial was conducted in several sites in Europe and was industry-sponsored. Risk of bias was moderate.

Improvement in LUTS was similar with solifenacin 6 mg with placebo in improving I-PSS scores (MD = -0.30) (low SoE). Urinary retention requiring catheterization was reported in one participant allocated to solifenacin 9 mg.

Evidence was insufficient regarding comparative withdrawals and withdrawal due to adverse effects. Dry mouth was reported more often with solifenacin (6%) versus placebo (0%).

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Solifenacin AB Combination Versus Placebo

Three 12-week trials (n=1857) compared a solifenacin-AB combination with placebo in men with LUTS and OAB symptoms (Table 7).[44,45,47] Trials combined solifenacin doses of 3, 6, or 9 mg with tamsulosin 0.4 mg. Two studies excluded patients with baseline postvoid residuals >150[45] or >200 ml,[44] respectively. Mean age of participants was 66 and mean baseline I-PSS score was 18 (range 18 to 19). Participants were predominantly white (99%). Two trials were conducted in Europe.[44,45] One trial enrolled participants from both Europe and the United States.[47] All were industry-sponsored and had low risk of bias.

Solifenacin-AB combination improved LUTS more than placebo (moderate SoE). Mean reduction in I-PSS scores with combination was 7.3 points compared with 5.7 points with placebo (WMD = -1.5). The magnitude of effect of combination therapy with 9 mg solifenacin appeared lower than with 6 mg. Combination therapy was similar to placebo in reducing I-PSS QoL scores (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 similar with combination therapy and placebo (insufficient SoE). Combination therapy was more likely to cause dry mouth and constipation than placebo.

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

Solifenacin, 3-6 mg Plus AB vs. Placebo *(3 RCT[44,45,47] N=1857)*	**# Trials (n)**	**Solifenacin/ AB Combo 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 dose) WMD = -1.50 [-1.80 to -1.20]	High
I-PSS QoL, *mean change from baseline*	1 (629)	-1.3	-0.9	SIMILAR MD = -0.40 [-0.70 to -0.10]	Low (unknown consistency)
Overall withdrawals	3 (1857)	9 (127/1350)	8 (42/507)	SIMILAR RR = 1.20 [0.46 to 3.13]	Low (low study limitations, imprecise)
Withdrawals due to adverse effects	3 (1857)	4 (50/1350)	2 (8/507)	RR = 2.17 [0.72 to 6.55]	Insufficient (imprecise)
Participants with ≥1 adverse effect	3 (1848)	28 (378/1341)	25 (128/507)	RR = 1.24 [0.99 to 1.55]	Insufficient (imprecise)

AB=alpha-blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Solifenacin AB Combination Versus AB Monotherapy

Seven 12-week trials[42-45,50,51,55] with 3147 participants contributed to the analysis of solifenacin plus tamsulosin versus tamsulosin monotherapy in men with LUTS and OAB symptoms (Table 8). Participants had a mean age of 66 and a mean baseline I-PSS score of 17 (range 14 to 19); and 96 percent were white. Five trials examined solifenacin, 5 mg[42,43,50,51,55] and two examined solifenacin, 6 mg.[44,45] Dosage of tamsulosin varied geographically. Three studies were conducted in South Korea[42,43,51] and one in Japan;[50] these trials used the lower than recommended daily 0.2 mg tamsulosin dose. One trial was conducted in the United States[55] and two in Europe,[44,45] these trials used a daily 0.4 mg tamsulosin dose. All trials except one[51] reported industry sponsorship; Seo et al. did not report a funding source. Overall risk of bias was moderate.

Combination therapy was similar to AB monotherapy in improving LUTS (moderate SoE). 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). Combination therapy lowered I-

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PSS QoL score more than tamsulosin, but the difference between groups was not clinically significant, indicating equivalence (moderate SoE). Evidence from four trials using solifenacin 3 to 9 mg[44,45,50,55] and reporting acute urinary retention showed no statistical difference in rates, but evidence was insufficient to draw conclusions due to the wide confidence intervals. 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.

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

Solifenacin, 5 or 6 mg Plus AB vs. AB *7 RCT; N=3147)*	# Trials (n)	Solifenacin/ AB Combo Mean or % (n/N)	AB Mono 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	SIMILAR WMD = -0.29 [-0.88 to 0.30]	Moderate (low-moderate study limitations)
I-PSS QoL, *mean change from baseline*	4 (1225)	-1.2	-0.9	SIMILAR WMD = -0.18 [-0.39 to -0.03]	Moderate (low-moderate study limitations)
Acute urinary retention-AUR	4 (2531)	1 (21/1615)	1 (2/916)	RR = 3.75 [0.71 to 19.79]	Insufficient (moderate study limitations, imprecise)
Overall withdrawals	7 (3147)	10 (203/2028)	11 (121/1119)	SIMILAR RR = 1.02 [0.74 to 1.41]	Low (low-moderate study limitations, imprecise)
Withdrawals due to adverse effects	5 (2900)	4 (71/1904)	3 (30/996)	SIMILAR RR = 1.27 [0.81 to 2.0]	Low (imprecise)
Participants with ≥1 adverse effect	5 (2918)	33 (623/1913)	29 (280/1005)	Greater with Combination RR = 1.21 [1.09 to 1.35]	Moderate (moderate study limitations)

AB=alpha blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Long-Term Adverse Events

We identified one study examining long-term adverse effects associated with solifenacin-AB combination therapy.[105] A select subset of participants from a previous RCT could participate in the 40-week open-label extension study (n=1066) for a combined treatment duration of 52 weeks. 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 events. Dry mouth, constipation, and dyspepsia were the most common long-term adverse events. Among 1066 patients, 86 serious adverse events occurred in 64 patients and included 3 deaths, 6 cases of acute urinary retention (0.7%), and 3 cases of intervertebral disc protrusion.

Fesoterodine

Fesoterodine AB Combination Versus AB Monotherapy

Two trials (n=990), one 12-weeks[53] and one 4-weeks in duration,[46] compared fesoterodine/AB combination therapy with AB monotherapy in men with LUTS and OAB symptoms (Table 9).[46,53] Mean age was 66 and mean baseline I-PSS score was 19 (range 16 to 19). Most participants were white (81%) in one trial that reported race/ethnicity.[53] Participants were randomized to daily doses of fesoterodine 4 mg combined with various ABs (most frequently tamsulosin 0.4 mg) versus the AB alone. One trial (n=943) was multinational[53] and the other (n=47) was conducted in Greece.[46] One trial reported industry sponsorship[53] and the other did not report sponsorship.[46] Overall risk of bias was moderate for one trial[53] and high for the other.[46]

Improvement in mean I-PSS scores was similar with fesoterodine-AB combination and AB monotherapy (low SoE). Acute urinary retention was infrequent in the one study that reported this outcome (≤1%) and only one participant in each study arm required catheterization.[53] Konstantinidis et al. did not report AUR.[46]

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Withdrawal for any reason, withdrawal due to adverse effects, and reporting at least one adverse effect were more frequent with combination treatments than with monotherapy (low SoE). 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[46,53] N=994)*	**# Trials (n)**	**Fesoterodin/ AB Combo Mean or % (n/N)**	**AB Mono Mean or % (n/N)**	**Results and Magnitude of Effect [95% CI]**	**Strength of Evidence (Rationale)**
I-PSS score, *mean change from baseline*	Konstantinidis, 2012 47 Kaplan, 2011 943	Konstantinidis, 2012 -2.4 Kaplan, 2011 -4.4	Konstantinidis, 2012 -0.7 Kaplan, 2011 -4.4	SIMILAR Konstantinidis, 2012 MD = -1.70 [-5.85 to 2.46] Kaplan, 2011 MD = 0.00 [-0.83 to 0.83]	Low (moderate study limitations, imprecise*)
Acute urinary retention-AUR	1 (947)	0.2 (1/474)	0.2 (1/473)	RR 1.00 [0.06 to 15.91]	Insufficient (moderate study limitations, imprecise, unknown consistency)
Overall withdrawals	1 (947)	15 (73/474)	10 (49/473)	Greater with fesoterodine RR 1.49 [1.06 to 2.09]	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]	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]	Low (moderate study limitations and unknown consistency)

AB=alpha blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

* One trial was small (n=47) and contributed little weight to the estimate

Oxybutynin

Oxybutynin AB Combination Versus AB Monotherapy

One 12-week trial (n=420) trial compared oxybutynin 10 mg tablets and AB combination therapy with AB monotherapy.[57] Individuals with a baseline postvoid 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%). 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 was conducted in the United States and reported industry sponsorship. Risk of bias was moderate.

Oxybutynin-AB combination therapy improved mean I-PSS scores more than AB monotherapy (WMD = -1.70) (insufficient evidence).

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

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Darifenacin

Darifenacin AB Combination Versus AB Monotherapy

Two 12-week trials (n=161) compared darifenacin/AB combination therapy with AB monotherapy in men with LUTS and OAB symptoms (Table 10).[39,49] Participants with a baseline postvoid residual of >150 ml were excluded. Mean age was 63 and mean baseline I-PSS score was 17. Race/ethnicity were not reported in either trial. Participants were randomized to daily doses of darifenacin 7.5 mg combined with doxazosin 4 mg[49] or tamsulosin 0.4 mg[39] versus the AB alone. One trial was conducted in Turkey[49] and the other in India.[39] Neither trial reported industry sponsorship. Risk of bias was low in one trial[39] and moderate in the other.[49]

Statistical differences between mean change in IPSS scores from baseline were unclear and strength of evidence was insufficient for this outcome. Overall, one trial reported acute urinary retention in four participants with combination therapy and one with AB monotherapy Withdrawals and withdrawals due to adverse effects were similar (insufficient SoE).

Table 10. Evidence overview: darifenacin/AB combination versus AB monotherapy

Darifenacin 7.5 mg vs. AB monotherapy *(2 RCT[39,49] n=161)*	# Trials (n)	Darifenacin/ AB Combo Mean or % (n/N)	AB Mono Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
IPSS/AUA-SS , *mean change from baseline*	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 -7.9 Ceylan, 2012 NR	Singh, 2015 -6.3 Ceylan, 2012 NR	Unclear Singh, 2015 MD = -1.6 [NR] Ceylan, 2012 MD = -3.47 [NR]	Insufficient (low-moderate study limitations, unknown precision, unknown consistency)
IPSS QoL, *mean change from baseline*	Ceylan, 2012 (101)	Ceylan, 2012 -1.8	Ceylan, 2012 -1.0	Unclear Ceylan, 2012 MD = -0.8 [NR]	Insufficient (low-moderate study limitations, unknown precision, unknown consistency)
Acute urinary retention	Singh, 2015 (60)	Singh, 2015 13 (4/30)	Singh, 2015 3 (1/30)	Singh, 2015 RR = 4.00 [0.47 to 33.73]	Insufficient (low-moderate study limitations, imprecision, unknown consistency)
Overall withdrawals	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 NR Ceylan, 2012 0 (0/51)	Singh, 2015 0 (0/30) Ceylan, 2012 0 (0/50)	Singh, 2015 RR not calculable Ceylan, 2012 RR = 0.98 [0.020 to 48.50]	Insufficient (low-moderate study limitations, imprecise, unknown consistency)
Withdrawals due to adverse effects	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 13 (4/30) Ceylan, 2012 0 (0/51)	Singh, 2015 0 (0/30) Ceylan, 2012 0 (0/50)	Singh, 2015 RR = 9.00 [0.51 to 160.18] Ceylan, 2012 RR = 0.98 [0.020 to 48.50]	Insufficient (low-moderate study limitations, imprecise, unknown consistency)

AB= alpha blocker; AUA-SS=American Urologic Association Symptom Scale; CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; NR=not reported; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio.

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Trospium

Trospium AB Combination Versus AB Monotherapy

One 12-week trial (n=58) compared trospium 45 mg daily doses with AB to AB monotherapy in men with LUTS and OAB symptoms.[48] Individuals with a baseline postvoid 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.

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

Mirabegron Versus Placebo

One 12-week trial (n=200)[65] assessed the efficacy of mirabegron at 50 mg (n=70) and 100 mg doses (n=65) with placebo (n=65) in males with LUTS attributed to 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 from baseline were -6.2, -4.8, and -5.0 in the 50 mg, 100 mg, and placebo groups. Differences between treatments were not significant. The information provided was insufficient for effect size calculation or pooling across dose levels for any outcome or adverse effect (insufficient SoE).

Mirabegron AB Combination Versus AB Monotherapy

One 8-week trial[64] (n=94) compared 50 mg of mirabegron combined with 0.2 mg tamsulosin versus tamsulosin monotherapy in males with LUTS attributed to BPH and OAB. It was conducted in Asia and used a 0.2 mg dose of tamsulosin. All patients were pretreated with tamsulosin. Patients with a postvoid residual >100 ml were excluded; mean age was 75. The study had high risk of bias (open label). The evidence was insufficient for mean change in I-PSS score and adverse effects.

PDE-5s

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

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Key Points

- Tadalafil improved short-term LUTS more than placebo (moderate SoE). Adverse effects were higher with tadalafil (high SoE).
- Tadalafil and tamsulosin were similarly effective in treating short-term LUTS. Rates of adverse effects were similar (moderate SoE). Withdrawals due to adverse effects were higher with tadalafil (moderate SoE).

Tadalafil

Tadalafil Versus Placebo

Ten eligible 12-week trials randomized men with LUTS attributed to BPH (n=3516) to tadalafil versus placebo (Table 11).[70,74,77,79,83-85,87,90,91] 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%).[79,83,84,87,90] Approximately 75 percent of participants had ED history. Subjects typically had to have an IPSS score of 13 or greater, a Qmax ranging from 4 to 15 mL/sec, and a post-void residual volume of less than 300 mL at baseline for inclusion. All participants in Egerdie et al. were sexually active and had BPH-LUTS and ED.[83] 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[90] and others evaluated 20 mg doses.[87,91] Four trials were multinational studies,[79,83,84,90] one was conducted in the United States and Canada,[87] one in the United States,[91] and four were conducted in Asia.[70,74,77,85] All trials reported industry sponsorship and had low to moderate risk of bias.

Tadalafil improved LUTS more than placebo (low to moderate SoE). One trial conducted a responder analysis, defined as a ≥3 point reduction from baseline I-PSS score.[91] Forty-nine percent responded with tadalafil compared with 36 percent with placebo (low SoE). Tadalafil 5 mg improved mean I-PSS scores from baseline more than placebo (WMD = -1.8) (moderate SoE). Tadalafil improved I-PSS scores by 5.5 points compared with 3.4 points with placebo. Both treatments reduced I-PSS scores greater than the MDD (3 points indicating slight improvement). Tadalafil 10 mg daily[90] and tadalafil 20 mg daily[87,90] showed larger effect sizes suggesting a dose-response relationship (test for subgroup differences I^2=76 percent, p=0.006). Seven trials reported BII.[74,79,83-85,90,91] Tadalafil 5 mg improved BII scores more than placebo (WMD -0.52), with both treatments showing improvements greater than MDD (-1.7 with tadalafil and -1.1 with placebo), which was greater than the MDD of 0.40 suggesting that most patients would notice benefits with tadalafil 5 mg. Tadalafil, 5 mg was better than placebo in improving BII scores (moderate SoE). Changes in I-PSS QoL were similar with tadalafil and placebo (WMD = -0.27) (high SoE). Mean changes from baseline were -1 and -0.7 points with tadalafil and placebo. Incidence of acute urinary retention was rare, reported in two participants with placebo in two trials.[74,90] No other indicators of disease progression/treatment failure were reported.

Study withdrawal for any reason was similar with tadalafil 5 mg and placebo (high SoE). However, participants allocated to tadalafil 5 mg were more likely to withdraw due to an adverse effect and report more than one adverse effect (high SoE); the absolute difference was small, two and six percent. 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). One trial included "increased erections secondary to sexual stimulation" based on specific questioning of

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an investigator as part of any treatment emergent adverse events.[91] However, only a small number of men taking taldalafil(7) or placebo(3) reported this outcome. A higher proportion of adverse effects at higher doses indicated a dose-response relationship (I^2=76%, p=0.006), but only three trials evaluated doses greater than 10 mg.[87,90,91] Four trials reported that dyspepsia was an adverse effect associated with tadalafil use (3% vs. 0% for placebo).[77,79,87,90] 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,[83,84] and one with placebo.[87]

Table 11. Evidence overview: tadalafil versus placebo

Tadalafil 5 mg vs. Placebo *(10 RCT*[70,74,77,79,83-85,87,90,91] *N=3516*	**# Trials (n)**	**Tadalafil 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 [-2.29 to -1.29]	Moderate (imprecise)
BII, *mean change from baseline*	7 (2161)	-1.7	-1.1	Favors tadalafil WMD = -0.52 [-0.78 to -0.26]	Moderate (imprecise)
I-PSS QoL, *mean change from baseline*	8 (2605)	-1.0	-0.7	SIMILAR (clinically) WMD = -0.27 [-0.31 to -0.23]	High
Overall withdrawals	9 (3082)	10.5 (115/1098)	10.5 (115/1093)	SIMILAR RR 1.00 [0.77 to 1.3]	High
Withdrawals due to adverse effects	9 (3082)	3.4 (37/1098)	1.6 (17/1093)	Greater with tadalafil RR = 1.80 [1.03 to 3.44]	High
Participants with ≥1 adverse effect	9 (3082)	28.7 (315/1098)	22.0 (240/1093)	Greater with tadalafil RR = 1.25 [1.09 to 1.44]	High

BII=Benign prostatic hyperplasia Impact Index; CI=confidence intervals; I-PSS=International Prostate Symptom Score; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Long-Term Adverse Events

Because no RCTs reported intermediate or long-term harms (i.e., followup longer than 12-weeks), we extracted longer term harms data from observational studies. We did not assess strength of evidence for these results and reported them for descriptive purposes.

Takeda, et al. conducted a 42-week, open-label extension study after the 3-month RCT for a combined treatment duration of 52 weeks, in which all participants took tadalafil 5 mg daily.[77] Nearly 59 percent of the 394 participants reported at least one adverse event and 9 percent withdrew due to an adverse event. Adverse events were similar to those reported during the double-blind phase. Serious adverse events were reported in 3 percent (11 participants) with the most 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.[107] 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 events and 58 percent experienced adverse events that first occurred or worsened during the extension. Only 2 of the 20 serious adverse events (those considered drug-related by investigators) were described (worsening of coronary artery disease and global amnesia). Common adverse events included dyspepsia (4%), gastro-esophageal reflux disease (4%), back pain (4%), sinusitis (3%), hypertension (3%), and cough (2%).

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Efficacy and Patient Demographic and Clinical Characteristics

Evidence from one RCT (n=175),[84] and a posthoc analysis of a previous trial (n=1056),[103] shows no difference in the effect of tadalafil 5 mg based on presence or severity or ED. Evidence from one pooled analysis (n=1500)[100] and one RCT (n=302) showed no difference in the effect of tadalafil 5 mg based on LUTS severity. Evidence from one pooled analysis (n=1500) showed 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) showed no difference in the effects of tadalafil or placebo based on previous use of ABs.[79]

Tadalafil AB Combination Versus AB Monotherapy

Four trials randomized males with BPH (n=224) to tadalafil combined with an AB or to AB monotherapy (Table 12).[71,72,75,88] Two 3-month trials compared tadalafil 10 mg daily[72] or 20 mg on alternate days[88] combined with alfuzosin 10 mg to alfuzosin 10 mg monotherapy. Two trials evaluated tadalafil combined with tamsulosin 0.4 mg versus tamsulosin 0.4 mg monotherapy: a 1-month trial evaluated tadalafil 5 mg daily[75] and a 4-month trial evaluated tadalafil 10 mg daily.[71] 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.[71,72,88] Subjects had to meet a minimum IPSS score at baseline, ranging from 8 to 12 or greater. Several trials did not include flowmetry data as inclusion criteria. For the trials that did, men were typically required to have a Qmax from 5 to 15 mL/sec. Trials were conducted in India,[71,72] Italy,[88] and Brazil.[75] All trials were open-label except Regadas et al.[75] and overall risk of bias therefore ranged from moderate to high.

Combination therapy was similar to AB monotherapy (Tadalafil 5-20 mg combined with AB was similar to AB monotherapy in improving mean I-PSS scores from baseline (WMD = -2.0), (insufficient SoE). Mean reductions in I-PSS scores were similar; 10.4 and 8.6 with combination and monotherapy. Improvement in mean I-PSS QoL scores was also similar with combination treatment and monotherapy, however only open label (high risk of bias) trials reported this outcome[71,72,88] (low SoE).

Evidence was insufficient for overall withdrawals and withdrawals due to adverse effects. 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.[81] 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.[81] There were no differences in withdrawals or withdrawals due to adverse effects, and no serious adverse effects were reported. No trials reported serious drops in blood pressure with combination therapy. Occasional cases of hypotention, which may be mild, were reported.

Table 12. Evidence overview: combined tadalafil/AB versus AB monotherapy

Tadalafil 5-20 mg Plus AB vs. AB Monotherapy (4 RCT[71,72,75,88] N=224)	# Trials (n)	Tadalafil/ AB Combo Mean or % (n/N)	AB Mono 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	WMD = -2.01 [-4.03 to -0.00]	Insufficient (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	3 (174)	-3.7	-3.3	SIMILAR (clinically) WMD = -0.44 [-0.73 to -0.15]	Low (high study limitations, confounding)

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Tadalafil 5-20 mg Plus AB vs. AB Monotherapy (4 RCT[71,72,75,88] N=224)	# Trials (n)	Tadalafil/ AB Combo Mean or % (n/N)	AB Mono Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Overall withdrawals	4 (224)	4 (5/112)	5 (6/112)	RR = 0.80 [0.12 to 5.29]	Insufficient (high study limitations, very imprecise)
Withdrawals due to adverse effects	4 (224)	4 (4/112)	3 (3/112)	RR = 1.13 [0.12 to 11.03]	Insufficient (high study limitations, very imprecise)

AB=alpha blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Tadalafil Combination Versus 5-ARI Monotherapy or 5-ARI/AB Combination

One 26-week (n=696) compared combined tadalafil 5 mg and finasteride 5 mg daily versus placebo and finasteride 5 mg daily.[73] Mean age was 64 and mean baseline I-PSS score was 17.3. Most participants were white (86%) and had ED history (65%). The trial had sites in the United States, Latin America, and Europe. The trial reported industry sponsorship, and overall risk of bias was low though the study duration of 26 weeks may be too short to demonstrate effectiveness of finasteride that may require longer follow-up.

Combined tadalafil/finasteride therapy improved mean I-PSS scores more than finasteride monotherapy (MD = -1.0) (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) (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). There was insufficient evidence regarding withdrawals due to adverse effects and the proportion reporting at least one adverse effect. 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.[80] 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 I-PSS scores by 5.4 points compared with 2.3 points with standard therapy/placebo (insufficient SoE). Combined tadalafil/standard therapy also improved I-PSS QoL scores more than standard therapy/placebo (MD = -0.6). 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)

Tadalafil Versus Tamsulosin

Four 3-month trials compared tadalafil 2.5, 5, or 10 mg daily with tamsulosin 0.2 or 0.4 mg daily (Table 13).[71,74,79,85] Mean age was 63 and mean baseline I-PSS score was 17.4 (range 16.8 to 20.6). Most participants were white (77%) in one multinational trial reporting race/ethnicity.[79]

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Most participants had an ED history.[71,79,85] The most frequently investigated dose level of tadalafil was 5mg; one trial studied a 2.5 mg dose[74,79,85] and one trial evaluated 10 mg.[71] Two trials conducted in Japan and Korea allocated participants to tamsulosin 0.2 mg daily, a dose lower than the 0.4 mg dose used in the United States.[74,85] The multinational trial[79] and the Indian trial evaluating tadalafil 10 mg[71] allocated participants to tamsulosin 0.4 mg. Three trials reported industry sponsorship.[74,79,85] Overall risk of bias was low to high for the four trials; Singh was open-label.[71]

Tadalafil 5 mg and tamsulosin were similar in improving mean I-PSS scores (moderate SoE) and I-PSS QoL (low SoE).

Evidence was insufficient for the outcomes of study withdrawal for any reason and proportion of participants reporting at least one adverse effect, but withdrawal due to adverse effects was higher with tadalafil (moderate SoE). Kim et al. reported that 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.[85] 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).[74] Oelke et al. reported two serious adverse effects with each treatment.[79] Singh et al. reported that no serious adverse effects occurring during the study period.[71]

Table 13. Evidence overview: tadalafil versus tamsulosin

Tadalafil 5 mg vs. Tamsulosin 0.2-0.4mg ***(4 RCT***[71,74,79,85] ***N=831)***	**# Trials (n)**	**Tadalafil Mean or % (n/N)**	**Tamsulosin Mean 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	SIMILAR WMD = 0.07 [-2.12 to 2.23]	Moderate (moderate study limitations)
BII, *mean change from baseline*	3 (731)	-1.5	-1.5	SIMILAR WMD -0.02 [-1.52 to 1.48]	Low (moderate study limitations, imprecise, inconsistent)
I-PSS QoL, *mean change from baseline*	3 (742)	-1.1	-1.1	SIMILAR WMD = -0.01 [-0.75 to 0.73]	Low (moderate study limitations, inconsistent)
Overall withdrawals	3 (742)	9.7 (36/373)	7.6 (28/369)	SIMILAR RR = 1.35 [0.30 to 6.05]	Low (moderate study limitations, imprecise)
Withdrawals due to adverse effects	3 (742)	2.9 (11/373)	1.1 (4/369)	Greater with tadalafil RR = 2.68 [1.09 to 6.60]	Moderate (moderate study limitations)
Participants with ≥1 adverse effect	3 (742)	25.2 (94/373)	24.4 (90/369)	SIMILAR RR = 0.99 [0.38 to 2.56]	Low (moderate study limitations, imprecise)

BII=Benign prostatic hyperplasia Impact Index; CI=confidence intervals; I-PSS=International Prostate Symptom Score; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Efficacy and Patient Demographic and Clinical Characteristics

One 12-week 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.[79]

Tadalafil Versus Alfuzosin

Two 3-month trials (n=93) compared tadalafil with alfuzosin 10 mg daily (Table 14).[72,88] 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.[72] Liguori et al. compared tadalafil 20 mg taken on alternate days with alfuzosin 10 mg daily.[88] Mean age of the participants

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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[72] and Italy.[88] 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) (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 SoE). Liguori et al. reported one participant discontinued treatment with tadalafil (back pain, headaches) versus three with alfuzosin (dizziness, constipation).[88] Kumar et al. reported two participants developed occasional headaches with tadalafil.[72] No serious adverse effects were reported.

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Table 14. Evidence overview: tadalafil versus alfuzosin

Tadalafil 10-20 mg vs. Alfuzosin 10 mg *(2 RCT*[72,88] *N=93)*	# Trials (n)	Tadalafil Mean or % (n/N)	Alfuzosin Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
I-PSS score, *mean change from baseline*	Kumar, 2014 50 Liguori, 2009 37	Kumar, 2014 -6.3 Liguori, 2009 -1.3	Kumar, 2014 -9.5 Liguori, 2009 -5.2	Favors alfuzosin Kumar, 2014 MD = 3.20 [1.71 to 4.69] Liguori, 2009 MD = 3.90 [0.72 to 7.08]	Low (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	Kumar, 2014 50 Liguori, 2009 37	Kumar, 2014 -2.4 Liguori, 2009 -1.0	Kumar, 2014 -3.2 Liguori, 2009 -1.3	Favors alfuzosin Kumar, 2014 MD = 0.80 [0.35 to 1.25] Liguori, 2009 MD = 0.30 [-0.35 to 0.95]	Low (high study limitations, imprecise)
Overall withdrawals	Kumar, 2014 50 Liguori, 2009 43	Kumar, 2014 0 (0/25) Liguori, 2009 10 (2/21)	Kumar, 2014 0 (0/25) Liguori, 2009 18 (4/22)	Kumar, 2014 RR not estimable Liguori 2009 RR = 0.52 [0.11 to 2.56]	Insufficient (high study limitations, imprecise)
Withdrawals due to adverse effects	Kumar, 2014 50 Liguori, 2009 43	Kumar, 2014 0 (0/25) Liguori, 2009 5 (1/21)	Kumar, 2014 0 (0/25) Liguori 2009 14 (3/22)	Kumar 2014 RR not estimable Liguori, 2009 RR = 0.35 [0.04 to 3.10]	Insufficient (high study limitations, imprecise)

CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio

Sildenafil

Sildenafil Versus Placebo

One 3-month trial (n = 369) compared sildenafil 50 mg (increasing to 100 mg at 2 weeks) with placebo.[92] 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%); all were experiencing ED in addition to LUTS attributed to BPH. The trial was conducted in the United States, reported industry sponsorship, and had low overall risk of bias.

Sildenafil improved mean I-PSS scores more than placebo (-6.3 vs. -1.9 points) (Low SoE). BII mean change was also greater with sildenafil (-2.0 points) than placebo (-0.9 points) (insufficient evidence). Mean change in I-PSS QoL was larger with sildenafil than placebo, -1.0 and -0.3 (insufficient evidence).

Evidence was insufficient for overall withdrawals, withdrawals due to adverse effects, and proportion reporting one or more adverse effects. Headache and dyspepsia were reported more frequently with sildenafil than placebo (11% vs. 3% and 6% vs. 1%, respectively). Two serious adverse effects were reported with sildenafil, including one severe acute cerebrovascular stroke.

Efficacy and 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.[104]

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Sildenafil AB Combination Versus AB Monotherapy

Four trials (n=281) compared sildenafil combined with an AB with AB monotherapy (Table 15).[76,78,86,93] The combinations studied varied. Two 3-month trials evaluated sildenafil combined with alfuzosin 10 mg, one used daily sildenafil 25 mg,[93] the other sildenafil 50 mg (dosing frequency not reported).[78] One 4-month trial evaluated sildenafil 50 mg combined with doxazosin 2 mg but the frequency of administration was not reported.[76] An 8-week trial evaluated sildenafil 25 mg taken 4 days per week combined with tamsulosin 0.4 mg daily.[86] 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.[76,86,93] Trials were conducted in Egypt,[76] Turkey,[78,86] and the United States.[93] 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 reductions in I-PSS scores were 5.4 with combination and 3.9 with monotherapy with both treatments exceeding MDD. However, the strength of evidence was insufficient due to the study limitations and imprecision in measurement.[76,78,93] 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.[86]

Evidence was insufficient for overall withdrawals and withdrawals due to adverse effects. Kaplan et al. reported three participants withdrew due to gastric upset and dizziness with combination therapy and two withdrew due to dizziness with alfuzosin.[93] No serious adverse effects were reported. Abolyosr et al. reported slight dizziness and blurring of vision, mainly in participants who took combined therapy.[76] Tuncel et al. did not report withdrawals or adverse effects.[86]

Table 15. Evidence overview: sildenafil/AB combination versus AB monotherapy

Sildenafil + AB vs. AB *(4 RCT[76,78,86,93] N=281)*	# Trials (n)	Sildenafil/ AB Combo Mean or % (n/N)	AB Monotherapy Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
I-PSS score, *mean change from baseline*	3 (233)	-5.4 Tuncel, 2010 -6.4	-3.9 Tuncel, 2010 -5.4	WMD = -1.73 [-4.76 to 1.30] 3 trials MD = -1 [CI NR] 1 trial	Insufficient (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	Ozturk, 2012 92 Tuncel, 2010 40	Ozturk, 2012 -1.8 Tuncel, 2010 -2.0	Ozturk, 2012 -1.7 Tuncel, 2010 -0.8	Ozturk, 2012 MD = -0.10 [-0.47 to 0.27] Tuncel, 2010 MD = -1.20 [-1.51 to -0.89]	Insufficient (high study limitations, imprecise inconsistent)
Overall withdrawals	Ozturk, 2012 100 Kaplan, 2007 41	Ozturk, 2012 10 (5/50) Kaplan, 2007 14 (3/21)	Ozturk, 2012 6 (3/50) Kaplan, 2007 10 (2/20)	Ozturk, 2012 RR = 1.67 [0.42 to 6.60] Kaplan, 2007 RR = 1.43 [0.27 to 7.67]	Insufficient (high study limitations, imprecise)
Withdrawals due to adverse effects	Ozturk, 2012 100 Kaplan, 2007 41	Ozturk, 2012 0 (0/50) Kaplan, 2007 14 (3/21)	Ozturk, 2012 0 (0/50) Kaplan, 2007 10 (2/20)	Ozturk, 2012 RR not estimable Kaplan, 2007 RR = 1.43 [0.27 to 7.67]	Insufficient (high study limitations, imprecise)

AB=alpha blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio

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Sildenafil Versus AB

Three trials (n=181) compared sildenafil versus an AB (Table 16).[76,86,93] One compared sildenafil 25 mg daily with alfuzosin 10 mg daily over 12 weeks[93] and compared sildenafil 25 mg taken 4 days per week with tamsulosin 0.4 mg daily over 8 weeks.[86] Abolyosr et al. compared sildenafil 50 mg with doxazosin 2 mg over 16 weeks; frequency of administration was not reported. The doxazosin 2 mg dose was generally lower that what is typically administered. Mean age of the participants was 61[76,86,93] and mean baseline I-PSS was 16.3 (range 14.9 to 17.1). All participants had ED history. Trials were conducted in Egypt,[76] Turkey,[86] and the United States.[93] 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.

Mean reduction in I-PSS scores was -2.2 with sildenafil and -3.2 with alfuzosin or doxazosin (insufficient SoE).[76,93] Mean reduction with sildenafil 25 mg was 4 points versus 5.4 points for tamsulosin 0.4 mg (insufficient SoE).[86]

Evidence was insufficient for overall withdrawals and withdrawals due to adverse effects. Kaplan et al. reported two participants using sildenafil withdrew due to flushing and dyspepsia and two using alfuzosin withdrew with dizziness.[93] Abolyosr et al. and Tuncel et al. did not report withdrawals.[76,86]

Table 16. Evidence overview: sildenafil versus AB monotherapy

Sildenafil 25-50 mg vs. AB (3 RCT[76,86,93] N=181)	# Trials (n)	Sildenafil Mean or % (n/N)	AB Mono Mean or % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
I-PSS score, *mean change from baseline*	Abolyosr, 2013 100 Kaplan, 2004 41	Abolyosr, 2013 -2.26 Kaplan, 2004 -2.0	Abolyosr, 2013 -3.36 Kaplan, 2004 -2.7	Abolyosr, 2013 MD = 1.10 [-0.70 to 2.90] Kaplan, 2004 MD = 0.70 [-1.72 to 3.12]	Insufficient (high study limitations, imprecise)
I-PSS QoL, *mean change from baseline*	1 (40)	-1.6	-0.8	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)	RR = 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)	RR = 0.95 [0.15 to 6.13]	Insufficient (high study limitations, unknown consistency, imprecise)

AB=alpha blocker; CI=confidence intervals; I-PSS=International Prostate Symptom Score; MD=mean difference; QoL=quality of life; RCT=randomized controlled trial; RR=risk ratio; WMD=weighted mean difference

Vardenafil

Vardenafil Versus Placebo

One trial compared vardenafil 10 mg twice daily to placebo.[89] 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%). Approximately 60 percent of participants reported ED or

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ejaculatory problems. The trial was industry sponsored, conducted in Germany, and had low risk of bias.

LUTS improved more with vardenafil than placebo (low SoE). Mean I-PSS scores decreased 5.9 with vardenafil and 3.6 with placebo, both exceeding the MDD.

Study withdrawal due to adverse effects and the proportion reporting one or more adverse effect (30% vs. 16%) was higher with vardenafil than placebo (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).

Vardenafil AB Combination Versus 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.[82] 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.

Mean reductions in I-PSS scores were 5.8 with combination and 3.7 with monotherapy, both achieving MDD (insufficient SoE).

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.

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Discussion

We conducted a systematic review with meta-analyses to assess the efficacy and comparative effectiveness of drugs recently proposed to treat LUTS attributed to 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 several newly used drugs or drug combinations (silodisin, fesoterodine/AB combination, and tadalafil) showed improved outcomes in LUTS attributed to BPH when compared with placebo but offered no benefit over traditional AB treatment, primarily with tamsulosin. Some drugs raised increased safety concerns, although the adverse effects were generally not severe and the event rate was low. These newly used drugs should therefore best be viewed as offering alternative treatment options rather than superior management options, although oftentimes associated with greater uncertainty with regards to associated harmsNewer and additional medications are typically associated with increased resource utilization that must be considered by the provider and patient in deciding on a course of treatment.

The new AB, silodosin, was more effective for LUTS attributed to BPH than placebo. However, it was not more effective than the older AB, tamsulosin, and associated with an increased rate of adverse events. The most common adverse effect associated with silodosin was abnormal ejaculation. This was consistent with reported adverse effects from longer term observational studies.

Anticholinergics (including tolterodine and solifenacin) combined with established ABs improved LUTS attributed to BPH more than placebo. However, neither tolterodine, solifenacin, nor fesoterodine combined with AB offered additional benefits in reducing LUTS over AB monotherapy. Evidence suggests that adverse effects with combination therapy may be higher than with AB monotherapy. AB combinations with oxybutynin, darifenacin, and trospium were also studied in eligible trials, but these comparisons provided insufficient evidence to draw conclusions with regard to any outcome or adverse effect.

Another new agent, the beta-3 agonist mirabegron that has primarily been used for OAB, has been tested in populations of men with LUTS attributed to 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 attributed to BPH. The associated adverse effects were higher based (high SoE). However, efficacy of tadalafil was similar or inferior to AB monotherapy (tamsulosin or alfuzosin, respectively). Trials did not report how the combination therapy affected blood pressure. Evidence was insufficient to assess efficacy and adverse effects of sildenafil and vardenafil. Evidence was insufficient to draw conclusions about the tadalafil and AB combination therapy compared with AB monotherapy in treating LUTS attributed to BPH. Most trials making this comparison were high risk of bias because they were open label or inadequately blinded and pooled estimates were imprecise. Reductions in blood pressure with this combination is a concern. FDA labeling suggests that patients be stable on AB therapy before starting PDE-5 inhibitor therapy and lower doses of the medications be used.[109] Our review did not find evidence of dangerous lowering of blood pressure. Occasional reports of hypotension were reported. However, this also occurs with AB monotherapy and data were too limited for comparison. The potential adverse effect should be taken into consideration by the provider and the patient.

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Using the established AHRQ strength of evidence rating system to describe our confidence in conclusions, we arrived at few "high" strength evidence assessments. Precision and study limitations components most frequently weakened the evidence base. Study limitations such as lack of blinding raised the concern for performance and detection bias. Imprecise estimates with lower and upper confidence interval estimates that would be interpreted differently were also common.

Our approach to random effects meta-analysis may also have contributed to the wider confidence intervals and greater imprecision. We initially pooled data with the classic DerSimonian-Laird random effects method. We revised our analysis because this method is likely to underestimate the error in parameter estimates, especially when the number of trials pooled is small.[110] Our data were not amenable to random effects estimation with a profile likelihood approach given the low level of statistical heterogeneity, so we opted to use the Hartung-Knapp-Sidik-Jonkman method. This method is conservative and lowers the possibility of false positive meta-analysis results common with DerSimonian-Laird, but can overestimate confidence intervals in some situations. Therefore, when one end of a confidence interval was close to a threshold and on the side of equivalence, we assessed the evidence as insufficient. Had the CI been slightly narrower, we likely would have drawn a conclusion with at least low strength of evidence.

Limitations

Our review sought to assess the short-, intermediate-, and long-term efficacy and comparative effectiveness of drugs newly used to treat LUTS attributed to BPH. All RCTs were of short duration and therefore provided no data on intermediate- and long-term outcomes and adverse effects. The lack of trials with longer durations prevented analysis of other important outcomes such as disease progression (measured as increases in I-PSS scores or need for surgical intervention). Given that LUTS attributed to BPH is a chronic and progressive condition, we can say little about treatments for the entire course of the disease. This may have implications for patients and clinicians decision whether to initiate these agents long term.

In the body of evidence summarized in this report, acute urinary retention was a relatively rare adverse effect. However, not only were most trials short in duration (12 weeks or less) but participants in trials of drugs known to affect bladder contractility often excluded those with higher postvoid residual urine volumes, thereby possibly removing patients at greatest risk and lowering the incidence of acute urinary retention in the trial population.

This review used prespecified patient important outcomes that were believed to reflect important to patients and critical to decisionmaking about treatment. These outcomes were typically measured with valid and reliable instruments, most commonly the I-PSS/AUA instruments. This instrument creates a summary score aggregating an individual's LUTS symptoms. We used established thresholds to determine clinical significance of the differences between treatments in these instrument scores. To the extent that patients or providers are interested in alleviating specific individual symptoms such as nocturia, thresholds indicating clinical significance are unclear and our report does not analyze that evidence.

While the instrument most commonly used across trials (I-PSS/AUA) has an anchor-based MDD, this was not used consistently in the original research to conduct responder analyses. Pooling responder analyses across trials would have provided the ideal efficacy outcome. Applying this MDD (3 point reduction from baseline) to the weighted mean difference between treatment groups in systematic review is not straightforward because it was derived from individual participant changes from baseline in response to treatment. Comparing differences between

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treatment groups differs by requiring the weighted mean difference to equal or exceed the mean MDD established from a pre- and post-treatment analysis can be misleading. This approach does not account for any placebo effect and can lead to similar conclusions when both or neither treatment group achieves MDD. We therefore tried to report mean changes from baseline per group in order to provide context regarding improvement relative to 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 and used guidance in interpreting the weighted mean difference. While we believe this to be the appropriate interpretation, statements such as "an appreciable number of patients" achieved clinically significant improvements suggested by the guidance may be considered vague and of limited value. Additionally, others suggest that a higher threshold be used to judge efficacy and comparative effectiveness. Blanker et al. suggests at least a moderate or marked improvement (i.e., 5 and 9 points on the I-PSS) should be the threshold.[111] The same WMD and this higher threshold would likely change our interpretation about whether an appreciable number of patients achieved benefits.

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 attributed to BPH symptoms. However, participant blinding in these trials is difficult in sexually active patients given the efficacy of PDE-5s in treating ED. We did not examine correlations between LUTS outcomes and ED outcomes because extracting ED outcomes was beyond the scope of this review.

There is growing interest in identifying which treatments for LUTS attributed to 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 provide no actionable information based upon patient demographic and clinical characteristics. Most of these analyses were posthoc, limiting the validity and reliability of the evidence.

Applicability

The body of evidence that we reviewed in this report is largely based on randomized clinical trials that enrolled patients that may differ 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 drugs known to decrease bladder contractility such as anticholinergics, participants were often screened for increased postvoid residuals and often excluded those above a certain threshold. The incidence of acute urinary retention in an unscreened population may therefore be higher.

Additionally, trials of anticholinergics and PDE-5s may not be applicable to the broader population of males with LUTS attributable to BPH. Enrollment criteria for these trials typically involved select symptoms (storage symptoms or ED) to be present. 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 drugs of sexual domain-related quality of life were outside the scope of this review. Most PDE-5 trials enrolled males who had not benefited from AB monotherapy and ED history. At the same time, long-term use that exceeds the time-horizon of randomized controlled trials may also increase the of adverse events such as hypotensive episodes, drug interactions, and

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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 were used in some trials.

Future Research Needs

Additional research would add valuable information on the treatment of LUTS attributed to BPH. Trials with longer duration of treatment and followup would provide valuable information on disease progression and long-term outcomes as it progresses with age. Longer time frames would provide important information to assess disease-related complications and drug-related adverse effects, which would be of great value to decisionmakers. 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 for individual patient. While we found little benefit from the newer drugs, it is possible that they provide benefits to select groups of patients. However, such benefits should be substantiated in appropriately designed that prospectively stratify patients accordingly to allow such inferences.

Trials, especially those conducted in Asian countries, using tamsulosin as a comparator often used 0.2 mg dosage. The standard dosage in the U.S. is 0.4 mg. We compared results of those trials with those using the U.S. standard dose of 0.4 mg and results were very similar.

Trials using drugs traditionally used to treat OAB or ED often enrolled males with LUTS attributed to BPH and the other condition. Results may apply most directly to those patients. Because these medications offered little additional benefit over traditional medications even in these populations, it is not likely results would be different in males with LUTS attributed solely to BPH.

Future studies would benefit from consistently conducting responder analysis (comparing the rates of response using MDD threshold) in addition to analysis of I-PSS scores. While providing complementary information, information from a responder analyses may provide data that are intuitively easier to understand, for example through NNT (number needed to treat) and NNH (number needed to harm), which can be calculated from dichotomous variables, but not continuous variables.

Conclusion

None of the drugs or drug combinations newly used to treat LUTS attributed to BPH showed outcomes superior to traditional AB treatment. Monotherapy with silodosin and tadalafil improved short-term LUTS more than placebo. Silodosin was equivalent to tamsulosin in improving LUTS and had higher adverse effects. Combination therapies adding an anticholinergic to an established AB offered no benefit over AB monotherapy in improving LUTS and often increased the rate of adverse effects. Silodosin and tadalafil were equivalent to tamsulosin in improving LUTS, but silodosin and tadalafil were associated with higher adverse effects. 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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101. Dmochowski R, Roehrborn C, Klise S, et al. Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial. J Urol 2013 Jan;189(1 Suppl):S135-40. PMID: 23234619.

102. Brock G, Broderick G, Roehrborn CG, et al. Tadalafil once daily in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men without erectile dysfunction. BJU Int 2013 Nov;112(7):990-7. PMID: 23937669.

103. Broderick GA, Brock GB, Roehrborn CG, et al. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia in men with or without erectile dysfunction. Urology 2010 Jun;75(6):1452-8. PMID: 20163842.

104. McVary KT, Siegel RL, Carlsson M. Sildenafil Citrate Improves Erectile Function and Lower Urinary Tract Symptoms Independent of Baseline Body Mass Index or LUTS Severity. Urology 2008 September;72(3):575-9. PMID: 18597830.

105. Drake MJ, Chapple C, Sokol R, et al. Long-term Safety and Efficacy of Single-tablet Combinations of Solifenacin and Tamsulosin Oral Controlled Absorption System in Men with Storage and Voiding Lower Urinary Tract Symptoms: Results from the NEPTUNE Study and NEPTUNE II Open-label Extension. Eur Urol 2015 Feb;67(2):262-70. PMID: 25070148.

106. Yoshimura K, Kadoyama K, Sakaeda T, et al. A survey of the FAERS database concerning the adverse event profiles of alpha1-adrenoreceptor blockers for lower urinary tract symptoms. Int J Med Sci 2013;10(7):864-9. PMID: 23781132.

107. Donatucci CF, Brock GB, Goldfischer ER, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU Int 2011 Apr;107(7):1110-6. PMID: 21244606.

108. Marks LS, Gittelman MC, Hill LA, et al. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. Urology 2009 Dec;74(6):1318-22. PMID: 19815265.

109. Kloner RA. Pharmacology and drug interaction effects of the phosphodiesterase 5 inhibitors: focus on alpha-blocker interactions. Am J Cardiol 2005 Dec 26;96(12B):42M-6M. PMID: 16387566.

110. Lau J, Terrin N, Fu R, eds. Expanded Guidance on Selected Quantitative Synthesis Topics. Methods Research Report. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-2007-10055-I.) AHRQ Publication No. 13-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

111. Blanker MH, van Deventer KR, Bijl D. Measuring symptomatic relief in men with lower urinary tract symptoms. BMJ. 2014;349:g6664. PMID: 25380756.

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Abbreviations

AB	Alpha blocker
ARI	Alpha reductase inhibitors
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
SOE	Strength of evidence
WMD	Weighted mean difference

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Appendixes

Contents

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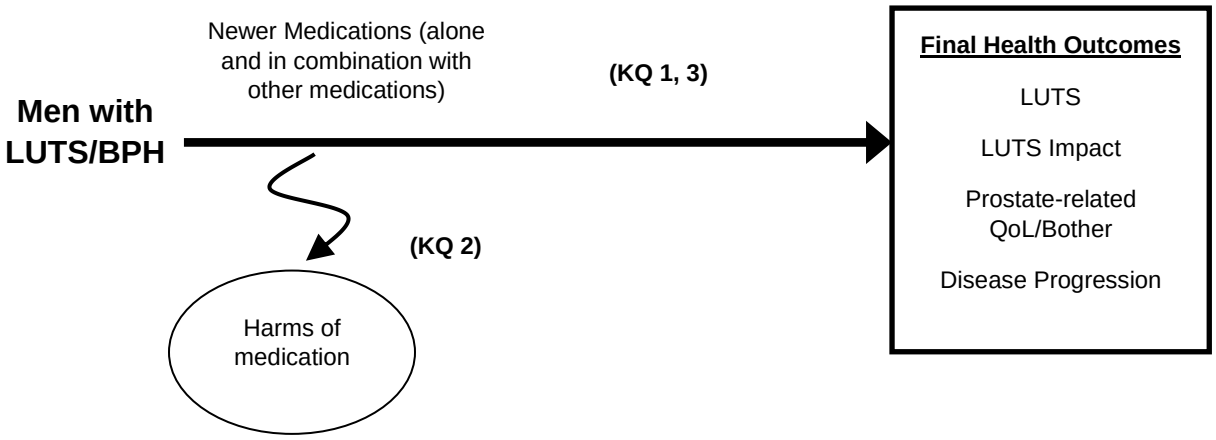
Appendix A. Analytical Framework and Search Strategies

Figure A1. Analytical framework for newer medications for LUTS/BPH



Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Search Strategies

BPH Medline RCTs SRs Harms

1. *Prostatic Hyperplasia/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
7. exp *Lower Urinary Tract Symptoms/
8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Urinary Bladder Neck Obstruction/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. silodosin.mp.
16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
19. oxybutynin.ti,ab.
20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.
32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.

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44. viagra.ti,ab.
45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. exp Review Literature as Topic/
61. or/55-60
62. cochrane.ab.
63. embase.ab.
64. (psychlit or psyclit).ab.
65. (psychinfor or psycinfo).ab.
66. or/62-65
67. reference list$.ab.
68. bibliograph$.ab.
69. hand search.ab.
70. relevant journals.ab.
71. manual search$.ab.
72. or/67-71
73. selection criteria.ab.
74. data extraction.ab.
75. 73 or 74
76. review/
77. 75 and 76
78. comment/
79. letter/
80. editorial/
81. animal/
82. human/
83. 81 not (82 and 81)
84. or/78-80,83
85. 61 or 66 or 72 or 77
86. 85 not 84
87. randomized controlled trials as topic/
88. randomized controlled trial/
89. random allocation/

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

90. double blind method/
91. single blind method/
92. clinical trial/
93. clinical trial, phase i.pt.
94. clinical trial, phase ii.pt.
95. clinical trial, phase iii.pt.
96. clinical trial, phase iv.pt.
97. controlled clinical trial.pt.
98. randomized controlled trial.pt.
99. multicenter study.pt.
100. clinical trial.pt.
101. exp Clinical trials as topic/
102. or/87-101
103. (clinical adj trial$).tw.
104. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
105. placebos/
106. placebo$.tw.
107. randomly allocated.tw.
108. (allocated adj2 random$).tw.
109. 103 or 104 or 105 or 106 or 107 or 108
110. 102 or 109
111. case report.tw.
112. case report.tw.
113. letter/
114. historical article/
115. 111 or 112 or 113 or 114
116. 110 not 115
117. 14 and 53
118. (ae or to or po or co).fs.
119. (safe or safety).ti,ab.
120. side effec*.ti,ab.
121. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
122. exp Product Surveillance, Postmarketing/
123. exp "Drug-Related Side Effects and Adverse Reactions"/
124. exp Adverse Drug Reaction Reporting Systems/
125. exp Clinical Trials, Phase IV as Topic/
126. exp Poisoning/
127. (toxicity or complication* or noxious or tolerability).ti,ab.
128. 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127
129. 117 and (86 or 116 or 128)
130. limit 129 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or

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festschrift or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts)
131. 129 not 130
132. limit 131 to "all child (0 to 18 years)"
133. limit 132 to "all adult (19 plus years)"
134. 131 not 132
135. 134 or 133
136. 135 and ("166".mp. or 128) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
137. 135 and 86

BPH Embase RCTs SRs Harms
March 25, 2015
1. *Prostate hypertrophy/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
7. exp *Lower Urinary Tract Symptom/
8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Bladder Neck stenosis/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. silodosin.mp.
16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
19. oxybutynin.ti,ab.
20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.
44. viagra.ti,ab.
45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. or/55-59
61. cochrane.ab.
62. embase.ab.
63. (psychlit or psyclit).ab.
64. (psychinfor or psycinfo).ab.
65. or/61-64
66. reference list$.ab.
67. bibliograph$.ab.
68. hand search.ab.
69. relevant journals.ab.
70. manual search$.ab.
71. or/66-70
72. selection criteria.ab.
73. data extraction.ab.
74. 72 or 73
75. review/
76. 74 and 75
77. comment/

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

78. letter/
79. editorial/
80. animal/
81. human/
82. 80 not (81 and 80)
83. or/77-79,82
84. 60 or 65 or 71 or 76
85. 84 not 83
86. randomized controlled trials as topic/
87. randomized controlled trial/
88. random allocation/
89. double blind method/
90. single blind method/
91. clinical trial/
92. (clinical adj trial$).tw.
93. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
94. placebos/
95. placebo$.tw.
96. randomly allocated.tw.
97. (allocated adj2 random$).tw.
98. or/86-97
99. case report.tw.
100. case study.tw.
101. letter/
102. historical article/
103. 99 or 100 or 101 or 102
104. 98 not 103
105. (ae or to or po or co).fs.
106. (safe or safety).ti,ab.
107. side effec*.ti,ab.
108. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
109. exp Product Surveillance, Postmarketing/
110. exp "Drug-Related Side Effects and Adverse Reactions"/
111. exp Adverse Drug Reaction Reporting Systems/
112. exp Clinical Trials, Phase IV as Topic/
113. exp Poisoning/
114. (toxicity or complication* or noxious or tolerability).ti,ab.
115. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114
116. 54 and (85 or 104 or 115)
117. limit 116 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
118. limit 117 to (adult <18 to 64 years> or aged <65+ years>)
119. 116 not 117
120. 119 or 118

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

121. limit 120 to (book or book series or conference abstract or conference proceeding or "conference review" or editorial or letter or note or short survey or trade journal)
122. 120 not 121
123. 122 and (104 or 115)
124. 122 and 85
125. 123 not 124
126. from 125 keep 1-461

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Appendix B. Risk of Bias Assessment Instrument and Instructions

Selection Bias	
Did method of randomization create biased allocation to interventions (inadequate randomization)?	
Were all randomized participants analyzed in the group to which they were allocated?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Did method of allocation create a biased allocation to interventions (inadequate allocation concealment)?	
Risk of selection bias (inadequate randomization or allocation concealment):	**[Low, Unclear, High]**
Performance Bias	
Was the care provider blinded to the intervention?	
Were the participants blinded to the intervention?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition and fidelity?	**[Low, Unclear, High]**
Detection Bias	
Were the outcome assessors blinded to the intervention?	
Questionnaire Derived Outcomes: Was the scale used to measure outcomes validated, reliable?	
Were outcomes measured in clinically meaningful ways?	
Were co-interventions avoided or similar?	
Was the timing of the outcome assessment similar in all groups?	
Were estimates appropriately corrected for multiple comparisons?	
Risk of detection bias due to lack of outcome assessor blinding, outcomes measurement, statistical analysis, power?	**[Low, Unclear, High]**
Attrition Bias	
Was attrition lower than 20%?	
Reasons for incomplete/missing data adequately explained?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	**[Low, Unclear, High]**
Reporting Bias	
Was a select group of outcomes reported (compared to methods section, protocol)?	
What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]	
Other Sources of Bias	
Are there other risks of bias? If yes, describe them in the Notes.	
Overall risk of bias assessment by outcome(s)	**[Low, Moderate, High] and explanation (1-2 sentences)**

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Appendix C. Excluded Studies

(Reason for exclusion appears in italics following each reference)

1. Abrams P, Kaplan S, De Koning Gans HJ, et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. Journal of Urology. 2006 Mar;175(3 Pt 1):999-1004; discussion PMID 16469601. *No outcomes of interest*
2. Ahmed AF, Maarouf A, Shalaby E, et al. The impact of adding low-dose oral desmopressin therapy to tamsulosin therapy for treatment of nocturia owing to benign prostatic hyperplasia. World Journal of Urology. 2015;33(5):649-57. PMID CN-01071213. *No interventions of interest*
3. Athanasopoulos A, Gyftopoulos K, Giannitsas K, et al. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. Journal of Urology. 2003 Jun;169(6):2253-6. PMID 12771763. *Not RCT*
4. Auerbach SM, Gittelman M, Mazzu A, et al. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. Urology. 2004 November;64(5):998-1003. PMID 2004480489. *Duration less than 4 weeks*
5. Bae JH, Kim SO, Yoo ES, et al. Efficacy and safety of low-dose propiverine in patients with lower urinary tract symptoms/benign prostatic hyperplasia with storage symptoms: A prospective, randomized, single-blinded and multicenter clinical trial. Korean Journal of Urology. 2011 April;52(4):274-8. PMID 2011251537. *No interventions of interest*
6. Bechara A, Romano S, Casabe A, et al. Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot study. Journal of Sexual Medicine. 2008 Sep;5(9):2170-8. PMID 18638006. *Not RCT*
7. Chen JH, Yu QW, Shen J, et al. Effectiveness of combined therapy with terazosin and tolterodine for patients with benign prostatic hyperplasia. Journal of Shanghai Jiaotong University (Medical Science). 2011;31(6):809-12. PMID 2011362895. *Not available in English*
8. Choi H, Kim JH, Shim JS, et al. Comparison of the efficacy and safety of 5-mg once-daily versus 5-mg alternate-day tadalafil in men with erectile dysfunction and lower urinary tract symptoms. International Journal of Impotence Research. 2015 Jan-Feb;27(1):33-7. PMID 24990200. *Not RCT*
9. De Rose AF, Giglio M, Traverso P, et al. Combined oral therapy with sildenafil and doxazosin for the treament of non-organic erectile dysfunction refractory to sildenafil monotherapy. International Journal of Impotence Research. 2002 Feb;14(1):50-3. PMID WOS:000173991500008. *Not BPH*
10. Dimitropoulos K, Gravas S. Solifenacin/tamsulosin fixed-dose combination therapy to treat lower urinary tract symptoms in patients with benign prostatic hyperplasia. Drug design, development & therapy. 2015;9:1707-16. PMID 25834406. *Not RCT*
11. Donatucci CF, Brock GB, Goldfischer ER, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU International. 2011 Apr;107(7):1110-6. PMID 21244606. *Not RCT*
12. Gacci M, Corona G, Vignozzi L, et al. Metabolic Syndrome and Benign Prostatic Enlargement: A Systematic Review and Meta-Analysis. BJU international. 2014. *Not RCT*
13. Gacci M, Sebastianelli A, Salvi M, et al. Tolterodine in the Treatment of Male LUTS. Current Urology Reports. 2015 Sep;16(9):531. PMID 26149965. *Not RCT*

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14. Giuliano F, Oelke M, Jungwirth A, et al. Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. Journal of Sexual Medicine. 2013 Mar;10(3):857-65. PMID 23346990. *No outcomes of interest*

15. Glina S, Roehrborn CG, Esen A, et al. Sexual function in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: results of a 6-month, randomized, double-blind, placebo-controlled study of tadalafil coadministered with finasteride. Journal of Sexual Medicine. 2015 Jan;12(1):129-38. PMID 25353053. *No outcomes of interest*

16. Guven EO, Balbay MD, Mete K, et al. Uroflowmetric assessment of acute effects of sildenafil on the voiding of men with erectile dysfunction and symptomatic benign prostatic hyperplasia. International Urology & Nephrology. 2009;41(2):287-92. PMID 18649004. *Duration less than 4 weeks*

17. Hakimi Z, Johnson M, Nazir J, et al. Drug treatment patterns for the management of men with lower urinary tract symptoms associated with benign prostatic hyperplasia who have both storage and voiding symptoms: a study using the health improvement network UK primary care data. Current Medical Research & Opinion. 2015 Jan;31(1):43-50. PMID 25333647. *Not RCT*

18. Jin Z, Zhang ZC, Liu JH, et al. An open, comparative, multicentre clinical study of combined oral therapy with sildenafil and doxazosin GITS for treating Chinese patients with erectile dysfunction and lower urinary tract symptoms secondary to benign prostatic hyperplasia. Asian Journal of Andrology. 2011 Jul;13(4):630-5. PMID 21602833. *No interventions of interest*

19. Johnson ITM, Markland AD, Goode PS, et al. Efficacy of adding behavioural treatment or antimuscarinic drug therapy to alpha-blocker therapy in men with nocturia. BJU International. 2013 July;112(1):100-8. PMID 2013381328. *No interventions of interest*

20. Kaplan SA. Re: Effect of tadalafil once daily on prostate blood flow and perfusion in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: a randomized, double-blind, multicenter, placebo-controlled trial. Journal of Urology. 2015 May;193(5):1592-3. PMID 25895781. *Not RCT*

21. Kraus SR, Dmochowski R, Albo ME, et al. Urodynamic standardization in a large-scale, multicenter clinical trial examining the effects of daily tadalafil in men with lower urinary tract symptoms with or without benign prostatic obstruction. Neurourology and Urodynamics. 2010 June;29(5):741-7. PMID 2010509134. *No outcomes of interest*

22. MacDiarmid SA, Anderson RU, Armstrong RB, et al. Efficacy and safety of extended release oxybutynin for the treatment of urge incontinence: an analysis of data from 3 flexible dosing studies. Journal of Urology. 2005;174(4 Pt 1):1301-5; discussion 5. PMID 16145407. *Not BPH*

23. Marks LS, Gittelman MC, Hill LA, et al. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. Urology. 2009 Dec;74(6):1318-22. PMID 19815265. *Not RCT*

24. Masumori N. Editorial Comment from Dr Masumori to Treatment satisfaction and clinically meaningful symptom improvement in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: Secondary results from a 6-month, randomized, double-blind study comparing finasteride plus tadalafil with finasteride plus placebo. International Journal of Urology. 2015 Jun;22(6):589. PMID 25827235. *Not RCT*

25. Mathias SD, Crosby RD, Nazir J, et al. Validation of the Patient Perception of Intensity of Urgency Scale in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia. Value in Health. 2014 Dec;17(8):823-9. PMID 25498777. *Not RCT*

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

26. Ng CF, Wong A, Cheng CW, et al. Effect of vardenafil on blood pressure profile of patients with erectile dysfunction concomitantly treated with doxazosin gastrointestinal therapeutic system for benign prostatic hyperplasia. Journal of Urology. 2008 Sep;180(3):1042-6. PMID 18639296. *Duration less than 4 weeks*

27. Nieminen T, Tammela TL, Koobi T, et al. The effects of tamsulosin and sildenafil in separate and combined regimens on detailed hemodynamics in patients with benign prostatic enlargement. Journal of Urology. 2006 Dec;176(6 Pt 1):2551-6. PMID 17085157. *Duration less than 4 weeks*

28. Nishizawa O, Yamaguchi O, Takeda M, et al. Randomized controlled trial to treat benign prostatic hyperplasia with overactive bladder using an alpha-blocker combined with anticholinergics. LUTS: Lower Urinary Tract Symptoms. 2011 April;3(1):29-35. PMID 2011215071. *No interventions of interest*

29. Oh-Oka H. Editorial Comment from Dr Oh-oka to Treatment satisfaction and clinically meaningful symptom improvement in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: Secondary results from a 6-month, randomized, double-blind study comparing finasteride plus tadalafil with finasteride plus placebo. International Journal of Urology. 2015 Jun;22(6):588. PMID 25827197. *Not RCT*

30. Perumal C, Chowdhury PS, Ananthakrishnan N, et al. A comparison of the efficacy of naftopidil and tamsulosin hydrochloride in medical treatment of benign prostatic enlargement. Urology annals. 2015;7(1):74-8. PMID CN-01049345. *Not RCT*

31. Porst H, McVary KT, Montorsi F, et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia.[Erratum appears in Eur Urol. 2011 Jun;59(6):1082]. European Urology. 2009 Oct;56(4):727-35. PMID 19409693. *No outcomes of interest*

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Appendix D. Supporting Tables and Figures: Silodosin

Table D1. Risk of bias assessments: silodosin trials

Study	Overall Risk of Bias Assessment	Rationale
Seki, 2015[1]	High	Randomization and concealment methods not reported, unblinded, groups similar at baseline except for prostate volume, high attrition
Choo, 2014[2]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for I-PSS storage, double-blinded, low attrition, PP and ITT analyses
Pande, 2014[3]	Low	
Yokoyama, 2012[4]	Moderate	Randomization and concealment methods not reported, groups similar at baseline, unblinded, completer analysis, attrition not reported by group
Chapple, 2011[5]	Low	
Watanabe, 2011[6]	High	Randomization and concealment methods not reported, open label crossover design with no washout, planned analysis not reported, high attrition, only completer baseline and results data reported
Yokoyama, 2011[7]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for PVR, unblinded, attrition moderate and similar between groups, unclear how missing data handled
Yu, 2011[8]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for prostate volume and acute urinary retention, double-blinded, attrition moderate and similar between groups, PP and ITT analyses
Miyakita, 2010[9]	High	Randomization and concealment methods not reported, drug dosages differed between groups, groups similar at baseline except for heart rate, unblinded, crossover design with no washout, planned analysis not reported, high attrition which differed by group, both baseline and outcome data reported for per protocol population only
Marks, 2009[10]	Low	
Kawabe, 2006[11]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for QoL, different group sizes, attrition not reported but only one patient excluded from analysis, outcome reporting unclear

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Table D2. Summary characteristics of BPH treatment, comparison, and population: silodosin trials

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total randomized	2940 (46 to 955)	9
Percentage randomized based on # screened	46 (32 to 78)	2
Received placebo, # randomized (% all randomized)	736 (25) (89 to 457)	3
Received tamsulosin[a], # randomized (% all randomized)	870 (30) (23 to 384)	8
Age of subjects, years	66 (62 to 71)	9
Percentage white race	61 (0[a] to 100)	9
Baseline I-PSS	19 (17 to 21)	9

[a] For crossover trials includes patients randomized to tamsulosin in the first phase
[b] All subjects from trials conducted in Asia (Japan, Korea, India: k=7; n=1022) presumed to be non-European white
I-PSS=International Prostate Symptom Score

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Table D3. Study characteristics: silodosin

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Seki, 2015[1]	T_1: Silodosin 8 mg qd T_2: Silodosin 4 mg bid	12 wk	I: Age ≥ 50 yr; LUTS, clinical BPH/OAB; IPSS ≥ 8; QOL ≥ 2; OAB symptom score ≥ 3; urgency score in OAB symptom score ≥ 2 E: Organic illness other than BPH (e.g. prostate cancer, acute or chronic prostatitis, bladder tumor, bladder calculus, bladder neck contracture, urethral stricture); surgical procedure of the lower urinary tract within 6 mo; indwelling urethral catheter; self-catheterization; active UTI; established or suspected neurogenic bladder	Mean age: 72 Race: NR Baseline I-PSS: 20.0
Choo, 2014[2] Korea N=424	T_1: Silodosin 8 mg qd T_2: Silodosin 4 mg bid	12 wk	I: Age ≥ 50 yr; LUTS/BPH; I-PSS ≥ 8; QoL-I ≥ 3; prostate volume ≥ 20 mL; Qmax <15 E: PVR ≥200 mL; history of prostatectomy, intrapelvic radiation, prostate cancer, or PSA >10 ng/mL; neurogenic bladder; active UTI; renal impairment, severe hepatic or cardiovascular disease; history of orthostatic hypotension; use of ABs within 2 wk or 5-ARIs within 3 mo	Mean age: 64 Race: NR Baseline I-PSS: 19.0
Pande, 2014[3] India N=61	T: Silodosin 8 mg qd C: Tamsulosin 0.4 mg qd	12 wk	I: Age > 50 yr; LUTS from BPH; I-PSS >7; treatment naïve E: LUTS but not BPH; acute retention of urine within 6 mo; elevated PSA, serious comorbidity; use of anticholinergic, androgenic or estrogenic medications; use of other α-adrenergic antagonists or diuretics; history of prostatic or urethral surgery, or substance abuse	Mean age: 62 Race: NR Baseline I-PSS: 18.4
Yokoyama, 2012[4] Japan N=46	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	13 wk	I: Age ≥50 yr; I-PSS ≥8; QoL-I ≥3 E: History of prostate cancer, neurogenic bladder, or urethral stricture; active UTI or other complications likely to affect micturition; PSA >4 ng/mL; negative prostatic biopsy	Mean age: 70 Race: NR Baseline I-PSS: 20.2
Chapple, 2011[5] Eisenhardt, 2014[12] Novara, 2014[13] Europe N=1336	T: Silodosin 8mg qd C_1: Placebo C_2: Tamsulosin 0.4 mg qd	12 wk	I: Age ≥50 yr; LUTS (I-PSS ≥13); BOO (Qmax 4-15 mL/s and voided volume ≥125 mL); compliance 80%-120% during placebo run-in E: Improvement in the I-PSS ≥25% during run-in; PVR ≥250 mL; intravesical obstruction from any cause other than BPH; history of any procedure for BPH, active UTI or recurrent UTIs; current prostatitis or chronic prostatitis; history of prostate or invasive bladder cancer, significant postural hypotension; use of 5-ARIs within 6 mo of an AB or phytotherapy within 2 wk	Mean age: 66 Race: 100% white Baseline I-PSS: 19.1
Watanabe, 2011[6] Japan N=102	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	4 wk	I: I-PSS ≥8; QoL-I ≥2; LUTS/BPH; previously untreated E: NR	Mean age: 70 Race: NR Baseline I-PSS: 17.3
Yokoyama, 2011[7] Japan N=90	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	12 wk	I: Age 50-80 yr; I-PSS ≥8 E: PSA >10, unless biopsy-negative for malignancy	Mean age: 71 Race: NR Baseline I-PSS: 18.4

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Yu, 2011[8] Taiwan N=209	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd; placebo	12 wk	I: Age ≥40 yr; I-PSS ≥13; HRQL ≥3; prostate volume ≥20 mL; Qmax <15 mL/s; voided volume ≥100 mL E: Previous prostate surgery, prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus; active UTI; PVR >250 mL; exposure to sex hormone within 3 mo; serum creatinine >2.0 mg/dL; severe liver or cardiovascular disease, severe hypotension; hypersensitivity; substance or alcohol abuse within 2 yr	Mean age: 67 Race: NR Baseline -I-PSS: 19.6
Miyakita, 2010[9] Japan N=97	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	4 wk	I: I-PSS ≥8; QoL-I ≥3; prostate volume ≥20 mL; void volume ≥100 mL; Qmax <15 mL/s E: lpha1-blocker use for hypertension, or for BPH within 2 mo; vardenafil use; inappropriate as judged by attending physician	Mean age: 69 Race: NR Baseline I-PSS: 17.4
Marks, 2009[10] Marks, 2013[14] Gittelman, 2011[15] Kapla,n 2011[16] Roehrborn, 2011[17] Eisenhardt, 2014[12] Novara, 2014[13] USA N=923	T: Silodosin 8 mg qd C: Placebo	12 wk	I: Age ≥50 yr; I-PSS ≥13; Qmax 4 -15 mL/s; PVR <250 mL E: Use of alpha-adrenoceptor antagonists or 5-ARIs; intravesical obstruction unrelated to BPH; bladder calculi; history of or current condition affecting bladder function; prior surgical intervention to relieve BPH or bladder neck obstruction; active UTI or history of recurrent UTI within 2 yr; prostatitis within 3 mo; BPH unrelated urinary retention within 3 mo; recurring prostatitis; prior or current prostate cancer or PSA >10 ng/mL; prior invasive bladder cancer; bladder catheterization or bladder or prostate instrumentation within 30 d and history of or current significant postural hypotension, including changes in systolic or diastolic blood pressure or heart rate, and lightheadedness, fainting, blurred vision, profound weakness, or syncope upon change in position	Mean age: 65 Race: 89% white Baseline I-PSS: 21.3
Kawabe, 2006[11] Homma, 2010[18] Japan N=631	T: Silodosin 4 mg bid C_1: Placebo C_2: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥50 yr; I-PSS of ≥8; QoL-I ≥3; LUTS/ BPH (by digital rectal examination or ultrasound); prostate volume ≥20 mL; Qmax <15 mL/s; voided volume ≥100 mL; PVR <100 mL; outpatients E: Use of antiandrogens within 1 yr; prostatectomy, intrapelvic radiation, or prostatic hyperthermia; prostate cancer or suspected prostate cancer; neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, severe bladder diverticulum, active UTI, serum creatinine ≥2.0 mg/dL, other complications affecting micturition; severe hepatic or cardiovascular disease; orthostatic hypotension	Mean age: 65 Race: NR Baseline I-PSS: 17.1

AB=alpha blocker; ARI=alpha-reductase inhibitor; bid=twice daily; BOO=bladder outlet obstruction; BPH=benign prostatic hyperplasia; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; HRQL=health-related quality of life; I=inclusion criteria; I-PSS=International Prostate Symptom Score; LUTS=lower urinary tract symptoms; mg=milligrams; mL=milliliters; ng=nanograms; NR=not reported; PSA=prostate-specific antigen; PVR=postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; QoL-I=International Prostate Symptom Score-QoL Item; s=seconds; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

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Table D4. Strength of evidence assessments: silodosin versus placebo

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Silodosin, 8 mg vs. placebo	I-PSS/AUA-SI , *mean change from baseline*	3 (1743)	Favors silodosin WMD = -2.68 [-3.91 to -1.44]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Moderate
	Responders ≥ 25% reduction in I-PSS scores	2 (819)	Favors silodosin Chapple, 2011 RR = 1.32 [1.12 to 1.54] Kawabe, 2006 RR = 1.51 [1.21 to 1.89]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	I-PSS QoL, reporting "delighted, pleased, or mostly satisfied'	2 (1494)	Favors silodosin Marks, 2009 RR = 1.42 [1.14 to 1.76] Chapple, 2011 RR = 1.29 [1.02 to 1.63]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	I-PSS QoL, *mean change from baseline*	1 (264)	MD = -0.60 [-0.92 to -0.28]	Low	Direct	Precise	Consistent (w/ dichotomous QoL)	Undetected[a]	NA	Moderate
	Overall withdrawals	2 (1494)	No Difference Marks, 2009 RR = 1.37 [0.92 to 2.03] Chapple, 2011 RR = 0.69 [0.39 to 1.24]	Low	Direct	Imprecise (CI not centered around 0)	Consistent	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	3 (1759)	Greater with silodosin RR = 2.41 [1.01 to 5.76]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	Participants with ≥1 adverse effect	3 (1757)	Greater with silodosin RR = 1.38 [1.05 to 1.81]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High

[a] We searched and screened results from clinicaltrials.gov. We identified five silodosin trials registered with clinicaltrials.gov; one registered trial could not be traced to a publication (NCT01222650); one included trial could not be traced to registration (Kawabe 2006); also identified a phase 2 trial in FDA documents that we did not identify a publication for. Results for I-PSS appeared consistent with those of published trials. We detected no publication bias.

I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Table D5. Strength of evidence assessments: silodosin versus tamsulosin

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Silodosin, 8 mg vs. tamsulosin 0.2 to 0.4 mg	I-PSS/AUA-, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	7 (1538)	WMD -0.63 [-1.62 to 0.36]	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	I-PSS/AUA -, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.2)	5 (738)	WMD -0.69 [-3.00 to 1.66]	Moderate	Direct	Imprecise	Consistent	Undetected[a]	Plausible Counfounding	Moderate
	I-PSS/AUA -, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.4)	Pande, 2014 (53) Chapple, 2011 (747)	Pande, 2014 MD = -0.70 [-2.42 to 1.02] Chapple, 2011 MD = -0.30 [-1.03 to 0.43]	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	Responders – 25% reduction in I-PSS scores (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	3 (1283)	RR 1.07 [0.91 to 1.26]	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	Responders, based on ≥25% reduction in total I-PSS score (Silodosin 8 mg vs. Tamsulosin 0.2)	2 (536)	Yu, 2011 RR = 1.05 [0.92 to 1.20] Kawabe, 2006 RR = 1.16 [1.02 to 1.33]	Moderate	Direct	Imprecise	Inconsistent	Undetected[a]	NA	Insufficient
	Responders, based on ≥25% reduction in total I-PSS score (Silodosin 8 mg vs. Tamsulosin 0.4)	1 (747)	RR = 1.02 [0.92 to 1.13]	Moderate	Direct	Precise	Unknown	Undetected[a]	NA	Low
	I-PSS QoL, reporting "delighted, pleased, or mostly satisfied'	1 (765)	RR 0.98 [0.83 to 1.15]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	I-PSS QoL, *mean change from baseline* (Silodosin	5 (728)	WMD -0.16 [-0.80 to 0.48]	Moderate	Direct	Precise	Inconsistent	Undetected[a]	Plausible Confounding	Moderate

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	8 mg vs. Tamsulosin 0.2 mg)									
	I-PSS QoL, *mean change from baseline* (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	1 (747)	MD = -0.30 [-1.03 to 0.43]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Low
	Overall withdrawals (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	4 (1125)	RR 1.05 [0.73 to 1.5]	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	Overall withdrawals (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	Pande, 2014 (53) Chapple, 2011 (747)	Pande, 2014 RR = 2.72 [0.60 to 12.42] Chapple, 2011 RR = 1.26 [0.71 to 2.23]	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	3 (1222)	RR 1.96 [1.04 to 3.71]	Moderate	Direct	Precise	Consistent	Undetected[a]	Plausible Confounding	Moderate
	Withdrawals due to adverse effects (Silodosin 8 mg vs. Tamsulosin 0.4 mg)	1 (747)	Chapple, 2011 RR = 2.02 [0.61 to 6.64]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect (Silodosin 8 mg vs. Tamsulosin 0.2 or 0.4 mg, pooled)	3 (1338)	RR 1.11 [0.95 to 1.29]	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified five silodosin trials registered with clinicaltrials.gov; one registered trial could not be traced to a publication (NCT01222650); one included trial could not be traced to registration (Kawabe 2006); also identified a phase 2 trial in FDA documents that we did not identify a publication for. Results for I-PSS appeared consistent with those of published trials. We detected no publication bias.

I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Analysis Figures for Silodosin

Figure D1. I-PSS scores, mean change from baseline: silodosin vs. placebo

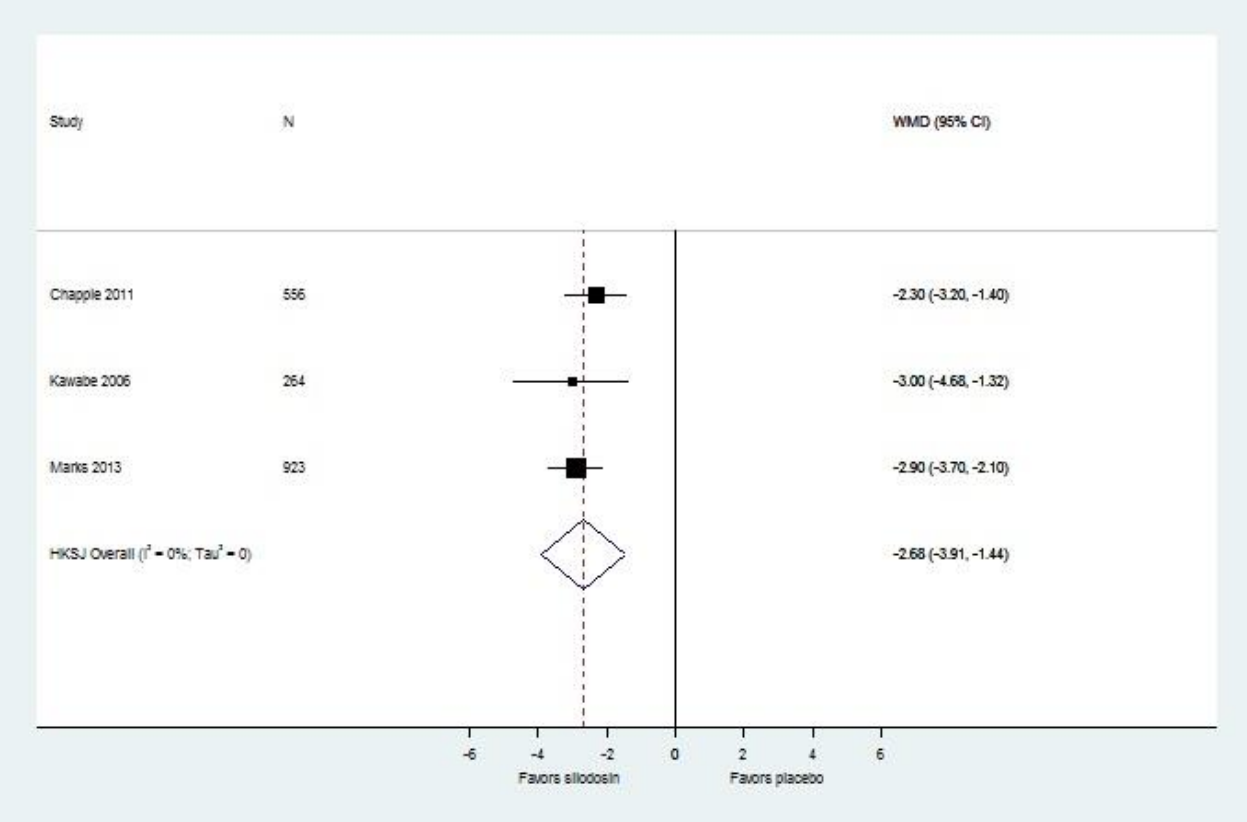

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Figure D2. I-PSS responders (≥25 decrease from baseline): silodosin vs. tamsulosin

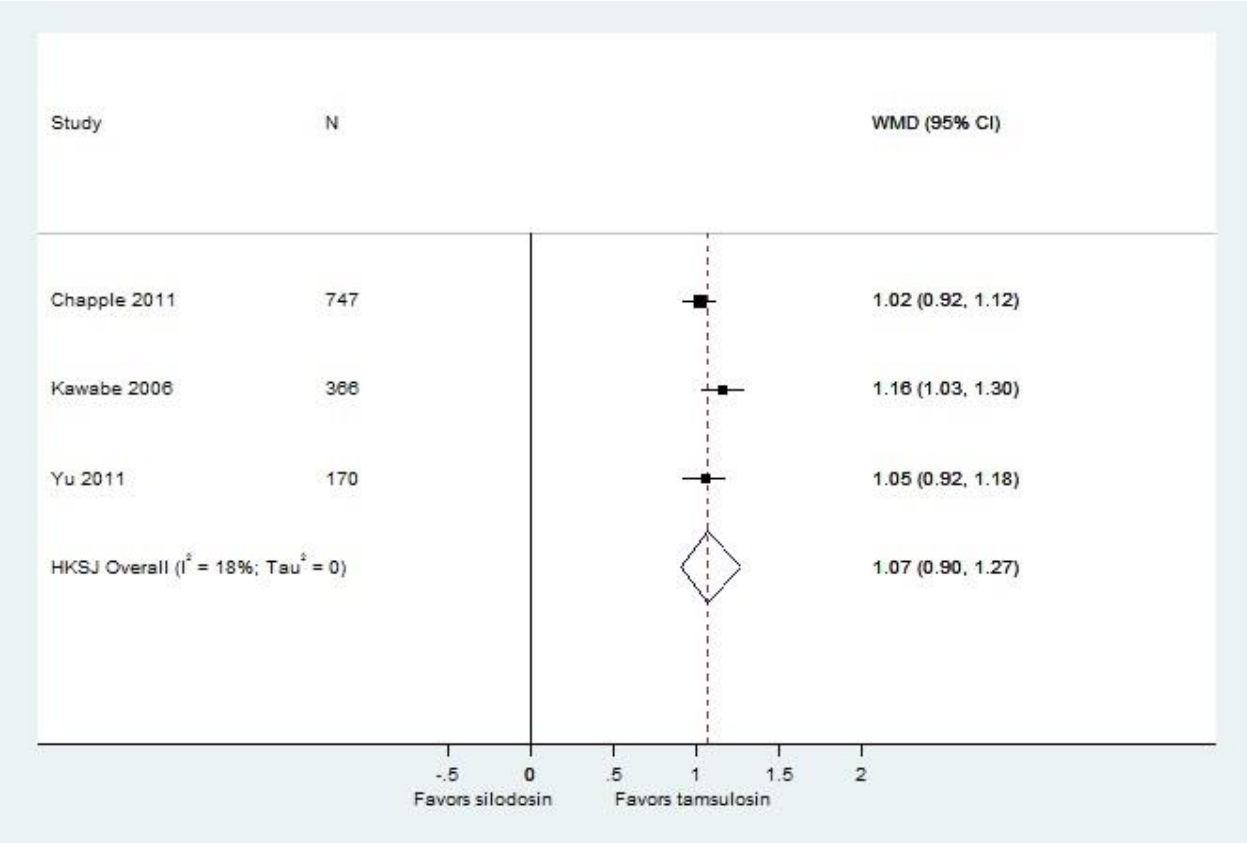

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Figure D3. I-PSS scores, mean change from baseline: silodosin vs. tamsulosin (0.2 and 0.4 mg doses)

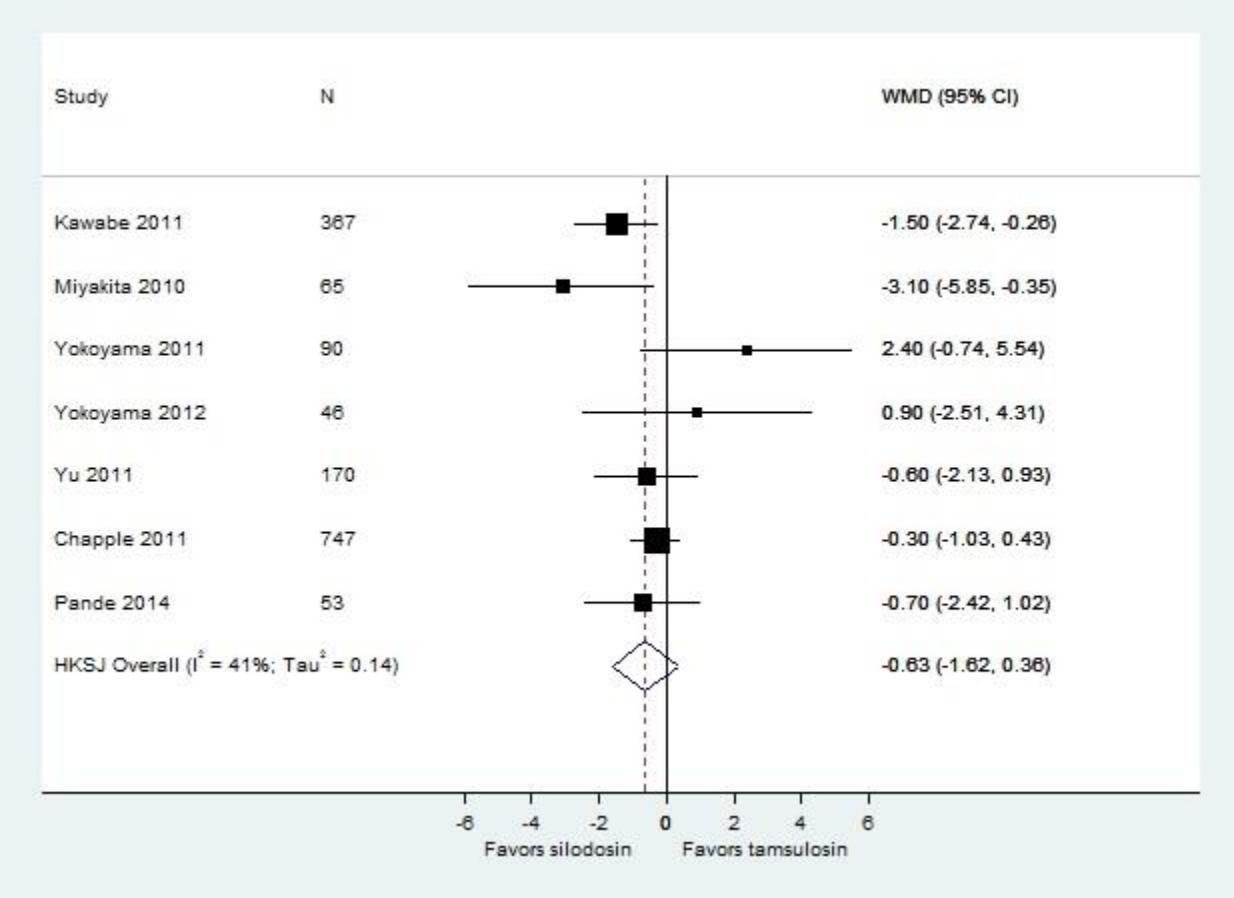

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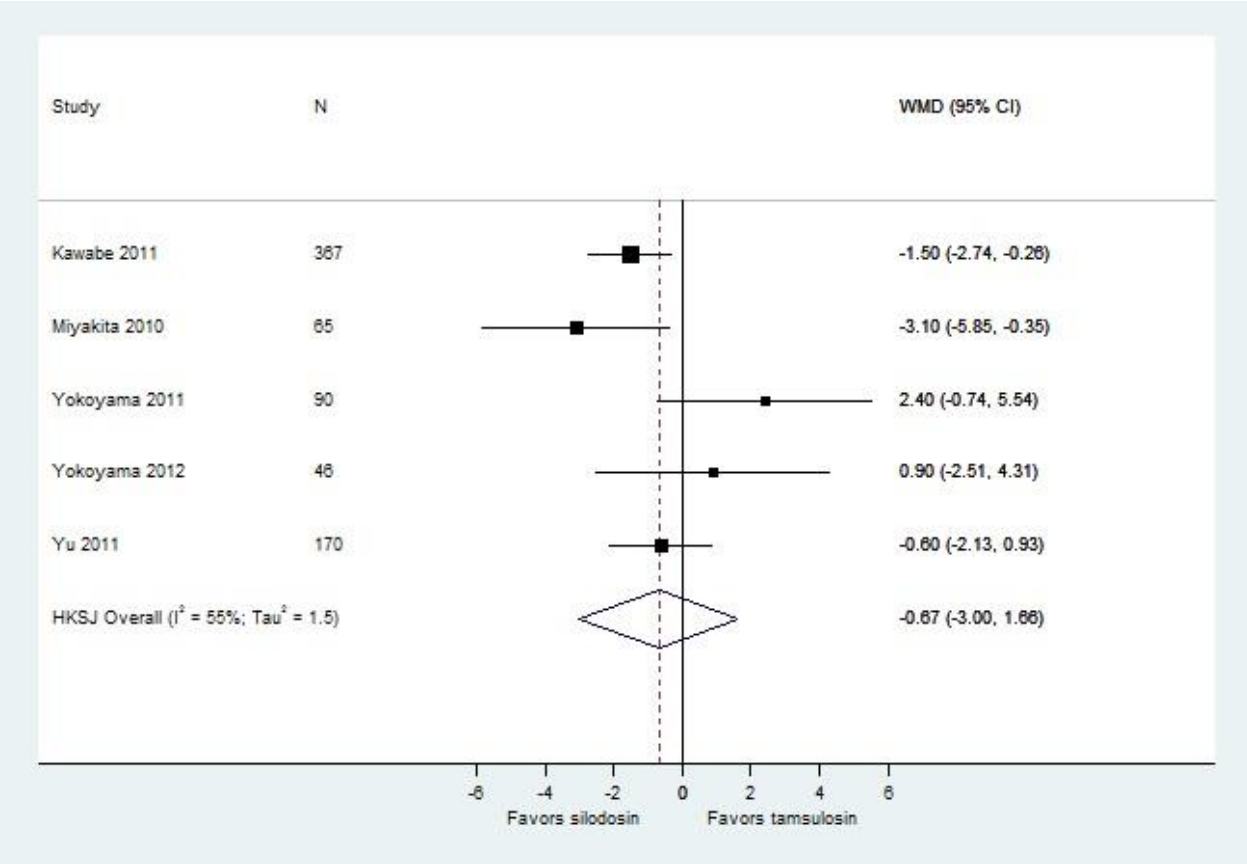
Figure D4. I-PSS scores, mean change from baseline: silodosin vs. tamsulosin (0.2 mg)



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Appendix E. Supporting Tables and Figures: Anticholinergics

Table E1. Risk of bias assessments: anticholinergic trials

Study	Overall Risk of Bias Assessment	Rationale
Liao, 2015[19]	High	Not blinded
Singh, 2015[20]	Low	
Ko, 2014[21]	High	Randomization and allocation methods unclear, open label, outcome assessor blinding not described, moderate attrition, attrition higher in treatment group
Lee, 2014[22]	Low	
Memon, 2014[23]	High	Participants purposively selected, blinding methods not described, outcome assessor blinding not reported, attrition not reported
Kaplan, 2013[24]	Low	
Van Kerrebroeck, 2013a[25]	Moderate	Randomization and allocation concealment unclear.
Van Kerrebroeck, 2013b[26]	Low	
Ceylan, 2012[27]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported, attrition not reported
Konstantinidis, 2012[28]	High	Randomization and allocation not mentioned, blinding not mentioned, attrition unclear, small sample size
Malkoc, 2012[29]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported, moderate attrition, patients with severe side effects excluded, small sample size
Chung, 2011[30]	High	Allocation methods unclear, blinding methods not reported
Kaplan, 2011[31]	Moderate	Randomization and allocation concealment unclear.
Lee, 2011[32]	Low	
Seo, 2011[33]	Moderate	Randomization and allocation methods unclear, blinding methods unclear, adverse events not reported
Yamaguchi, 2011[34]	Low	
Chapple, 2009[35]	Low	
Kaplan, 2009[36]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported
MacDiamid, 2008[37]	Low	
Kaplan, 2006[38]	Low	

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Table E2. Summary of anticholinergic trials: tolterodine

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total randomized	1777 (70 to 879)	4
Percentage randomized based on # screened	66 (57 to 77)	3
Received placebo, # randomized (% all randomized)	222 (12)	1
Received alpha-blocker, # randomized (% all randomized)	664 (37) (35 to 323)	4
Age of subjects, years	63 (61 to 65)	4
Percentage white race	67 (0[a] to 83)	4
Baseline I-PSS	20 (19 to 24)	4
Percentage with over active bladder symptoms	100	4
Percentage with erectile dysfunction	27	1

[a] All subjects from trials conducted in Asia (Korea, India: k=2; n=246) presumed to be non-European white
I-PSS=International Prostate Symptom Score

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Table E3. Summary of anticholinergic trials: solifenacin

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total randomized	3710 (60 to 1334)	7
Percentage randomized based on # screened	80 (56 to 93)	5
Received placebo, # randomized (% all randomized)	433 (12) (92 to 341)	2
Received tamsulosin[a], #randomized (% all randomized)	1106 (30) (30 to 327)	7
Age of subjects, years	66 (58 to 70)	7
Percentage white race	70 (0[a] to 99.6)	7
Baseline I-PSS	17 (14 to 19)	7
Percentage with over active bladder symptoms	100[b]	3
Percentage with erectile dysfunction	56 (28 to 100)	3

[a] All subjects from trials conducted in Asia (Korea, Japan: k=4; n=1041) presumed to be non-European white

[b] The inclusion criteria or baseline parameters for 3 additional trials noted participants were to have ≥8 micturitions/day and ≥1 or 2 urgency episodes/day

I-PSS=International Prostate Symptom Score

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Table E4. Summary of anticholinergic trials: fesoterodine

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total randomized	990 (47 to 943)	2
Percentage randomized based on # screened	70 (27 to 71)	2
Received placebo, # randomized (% all randomized)	0	2
Received alpha-blocker, # randomized (% all randomized)	496 (50) (23 to 473)	2
Age of subjects, years	66 (64 to 66)	2
Percentage white race	81	1
Baseline I-PSS	19 (16 to 19)	2
Percentage with over active bladder symptoms	100	2
Percentage with erectile dysfunction	NR	

I-PSS=International Prostate Symptom Score

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Table E5. Characteristics of BPH treatment, comparison, and population: anticholinergic trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Liao, 2015[19] Taiwan N=202	T: Tolterodine 4 mg C: Doxazosin 4 mg	12 wk	I: Age ≥40 yr; I-PSS ≥8; predominant storage LUTS (I-PSS-S ≥I-PSS-V); PVR ≤250 mL E: PSA level >10 ng/mL; history of urinary retention, urodynamically proven detrusor underactivity, active UTI, urinary stone, documented genitourinary cancer, or previous transurethral surgery; antimuscarinics or 5a-reductase inhibitors within 6 mo	Mean age: 69 Race: NR Baseline I-PSS: 11.5
Singh, 2015[39] India N=60	T: Darifenacin 7.5 mg qd; tamsulosin 0.4 mg C: Tamsulosin 0.4 mg qd; placebo	8 wk	I: LUTS/BPH with at least one OOB symptom: urinary frequency (>8 micturitions/d), nocturnal frequency (> 2/d) urgency > 1/d, with or without urge incontinence E: Qmax < 5 mL/s; voided volume < 50 mL/s; PVR >150 mL/s (by ultrasound); progressively rising PVR; renal failure; untreated UTI; vesical stones; contraindications to alpha-1-adrenergic receptor antagonist or antimuscarinic agent	Mean age: 61 Race: NR Baseline I-PSS: 18.9
Ko, 2014[21] Korea N=187	T: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg	12 wk	I: Age >40 yr; LUTS (I-PSS >12); urinary frequency (≥8/d), urgency (≥1/d), and symptoms on 3 d voiding diary E: Urologic malignancy; UTI; medical renal disease; medical liver disease; clinically significant BOO (residual urine >100 mL)	Mean age: 61 Race: NR Baseline I-PSS: 19.3
Lee, 2014[22] Korea N=156	T: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥50 yr; total I-PSS ≥14; IPPS-V ≥8; I-PSS-S ≥6; QoL-I ≥3; micturition frequency ≥8 micturitions per 24 hr; urgency (≥1 micturition with urgency rating 3 per 24 hr); prostate volume ≥20; Qmax ≤15 mL/s; voided volume ≤125 mL E: Neurogenic bladder dysfunction; confirmed prostate cancer; acute or chronic urinary retention status; acute or chronic prostatitis within the previous 3 mo; PSA levels >10 ng/mL; history of recurrent UTI or bladder stones; previous BPH treatment; previous surgical intervention related to BOO	Mean age: 61 Race: NR Baseline I-PSS: 17.9
Memon, 2014[23] Pakistan N=70	T: Tolterodine 2 mg bd; alfuzosin 10 mg hs C: Alfuzosin 10 mg hs	12 wk	I: Age >40 yr; BPH diagnosed on ultrasound scan having OAB symptoms; I-PSS = 15-30 for >3 mo E: PVR >100 mL; Qmax <5 mL; conditions affecting bladder function like multiple sclerosis, spinal cord injury, or Parkinson's disease; history of Parkinson's disease, prostatic cancer, indwelling catheter, or use of anti-muscarinic or Abs	Mean age: NR Race: NR Baseline I-PSS: 23.7
Kaplan, 2013[24] USA N=222	T: Solifenacin 6 mg; tamsulosin 0.4 mg T_2: Solifenacin 9 mg; tamsulosin 0.4 mg C: Placebo	12 wk	I: Age ≥45 yr; completed 3 d micturition diary; voiding and storage LUTS ≥3 mo; I-PSS ≥8; BOOI ≥20; Qmax ≤12 mL/s, maximum voided volume ≥120 mL E: Indwelling urinary catheter; history of urinary retention >12 mo, carcinoma or pelvic radiation therapy, neurogenic bladder, chronic inflammation, stone in bladder/ureter, outflow tract obstruction, uncontrolled narrow-angle glaucoma,	Mean age: 64 Race: 98% white Baseline I-PSS: 17.8

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
			myasthenia gravis, urinary or gastric retention, bladder neck surgery, or diabetic neuropathy; contraindicated for use of anticholinergics; current UTI; recurrent UTI >3 episodes within 12 mo; previous/planned prostate surgery; hypersensitivity to solifenacin succinate or other anticholinergics, or tamsulosin hydrochloride	
Van Kerrebroeck, 2013a[25] Netherlands N=937	T_1: Solifenacin 3 mg; tamsulosin 0.4 mg T_2: Solifenacin 6 mg; tamsulosin 0.4 mg T_3: Solifenacin 9 mg; tamsulosin 0.4 mg T_4: Solifenacin 3 mg T_5: Solifenacin 6 mg T_6: Solifenacin 9 mg C_1: Tamsulosin 0.4 mg C_2: Placebo	12 wk	I: I-PSS ≥13; Qmax = 4–15 mL/s; volume voided during free flow ≥120 mL E: PVR >200 mL; UTI; history of specific urinary conditions (including urinary retention); previous bladder neck or prostate surgery	Mean age: 65 Race: 100% white Baseline I-PSS: 18.5
Van Kerrebroeck, 2013b[26] Netherlands N=1334	T_1: Solifenacin 6 mg; tamsulosin 0.4 mg T_2: Solifenacin 9 mg; tamsulosin 0.4 mg C_1: Placebo C_2: Tamsulosin 0.4 mg	12 wk	I: Age ≥45 yr; storage and voiding symptoms; LUTS ≥3 mo; I-PSS ≥ 13; Qmax = 4–12 mL/s; voided volume ≥120 mL during free flow; ≥2 urgency episodes per 24 hr (PPIUS grade 3 or 4); ≥ 8 micturitions per 24 hr before randomization E: Ultrasound-estimated prostate weight ≥75 g; UTI; history of specific urinary conditions; PVR >150 mL	Mean age: 65 Race: 99% white Baseline I-PSS: 18.7
Ceylan, 2012[27] Turkey N=101	T: Darifenacin 7.5 mg; doxazosin 4 mg C: Doxazosin 4 mg	12 wk	I: Age >50 yr; I-PSS >12; >8 micturitions per 24 hr; urgency >3 episodes per 24 hr; some moderate problems related to their bladder condition reported E: PVR >150 mL; Qmax <5 mL/s; previous prostatic surgery; PSA >10 ng/mL; bladder stone; diverticula; UTI; urethral stricture; neurogenic bladder; diabetes mellitus; previously treated with α-adrenergic antagonist, antimuscarinic agents, or diuretic medicine; histopathological prostate cancer diagnosis; PSA = 4-10 ng/mL; transrectal ultrasound guided prostatic biopsy	Mean age: 64 Race: NR Baseline I-PSS: 16.3
Konstantinidis, 2012[28] Greece N=47	T: Fesoterodine 4 mg; tamsulosin 0.4 mg C: Tamsulosin 0.4 mg	6 wk	I: Age ≥50 yr; LUTS storage symptoms from suspected OAB and BOO E: PVR ≥200 mL; I-PSS <12; Qmax ≤10 mL/s; prostate volume ≤60 cm^3; PSA ≥4 ng/mL; history of neurological diseases, other medications for LUTS (e.g. 5 α-reductase agents), bladder surgical interventions, AUR, glaucoma, and hepatic or renal failure	Mean age: 64 Race: NR Baseline I-PSS: 16.0
Malkoc, 2012[29] Turkey N=58	T: Trospium chloride 45 mg; terazosin 5 mg C: Placebo; terazosin 5 mg	12 wk	I: Age >45 yr; OAB symptoms (urgency and mean urinary frequency ≥8 times per 24 hr with or without urinary incontinence) E: History of neurologic diseases, previous use of anticholinergic or alpha adrenergic blocker, PVR ≥100 mL, prostate volume >50 mL; history of AUR	Mean age: 58 Race: NR Baseline I-PSS: 15.3

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
			requiring catheterization; prostatic surgery; prostate cancer; PSA >4 ng/mL; UTI; diabetes	
Chung, 2011[30] Taiwan N=137	T: Tolterodine ER 4 mg qd; doxazosin ER 4 mg qd and or dutasteride 0.5 mg qd C: Doxazosin ER 4 mg qd and or dutasteride 0.5 mg qd	52 wk	I: Age ≥70 yr; I-PSS >8; I-PSS-S >5; QoL-I >3; prostate volume >20 mL; Qmax <15 mL/s; urodynamic confirmed BPH/BOO E: Abnormal digital rectal examination; history of medical therapy or surgery for BPH; past or current use of ABs, finasteride or antimuscarinic agents; UTI; indwelling urethral catheter and previous urinary retention; PVR >250 mL; history of malignancy of genitourinary tract, neurological diseases (stroke, diabetes, multiple sclerosis, Parkinson's disease), symptomatic congestive heart failure, or chronic kidney disease	Mean age: 75 Race: NR Baseline I-PSS: NR
Kaplan, 2011[31] USA N=943	T: Flexible-dose fesoterodine 4 or 8 mg alpha blocker C: Placebo; alpha blocker	12 wk	I: Age ≥40 yr; use of ABs for LUTS >6 wk; storage symptoms of frequency and urgency (≥8 micturitions and ≥3 urgency episodes per 24 hr); PPBC ≥3 E: PVR >200 mL; poor tolerability of ABs; history of AUR requiring catheterization; history or evidence of clinically significant BOO; prostate cancer; PSA >10 ng/mL; neurological conditions (stroke, multiple sclerosis, spinal cord injury, Parkinson's disease); UTI; >3 episodes UTI in prior 12 mo; history of prostatic, urethral, or bladder surgery; antimuscarinic within 3 wk or 5-ARIs within 6 mo	Mean age: 66 Race: 81% white Baseline I-PSS: 19.0
Lee, 2011[32] Korea N=176	T_1: Tolterodine SR 4 mg; doxazosin GITS 4 mg T_2: Doxazosin GITS 4 mg; placebo	4 wk	I: Age ≥50 yr; I-PSS ≥14; I-PSS-V ≥8; I-PSS-S ≥6; QoL-I ≥3; ≥8 micturition per 24 hr; ≥1 micturition with urgency rating 3 per 24 hr; prostate volume ≥20; Qmax ≤15 mL/s; voided volume ≥125 mL E: History of neurogenic bladder dysfunction, prostate cancer, acute or chronic urinary retention, acute or chronic prostatitis within the prior 3 mo; PSA >10 ng/mL; recurrent UTI or bladder stones; previous medication history for BPH; previous surgical intervention related to BPO	Mean age: 61 Race: NR Baseline I-PSS: 21.4
Seo, 2011[33] Korea N=56	T: Solifenacin 5 mg qd; tamsulosin 0.2 mg qd C: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥40 yr; concurrent LUTS and ED; I-PSS >12; QoL-I >3; IIEF-5 <20 E: Anti-androgens, sex hormone agents, PDE-5s in prior 4 wk; prostate or urethra surgery; urethral stricture; UTI; prostatitis; prostate cancer; bladder cancer; PSA >4 mg/dL; severe renal or hepatic dysfunction; PVR >100 mL	Mean age: 58 Race: NR Baseline I-PSS: 17.8
Yamaguchi, 2011[34] Japan N=638	T: Solifenacin 2.5 mg; tamsulosin 0.2 mg T_2: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg; placebo	12 wk	I: Age ≥50 yr; LUTS and residual OAB symptoms; urgency episodes ≥2 per 24 hr; micturitions ≥8 per 24 hr; Qmax ≥5 mL/s; PVR ≥50 mL E: Polyuria (≥3000 mL per 24 hr); urethral stricture; bladder neck stricture; prostate cancer or other malignancy; any disease other than LUTS that would affect voiding; surgery affecting urinary tract function; contraindicates for antimuscarinic or alpha-1 blocker therapy	Mean age: 70 Race: NR Baseline I-PSS: 13.5

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Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Chapple, 2009[35] North America, Asia, Europe, South Africa N=652	T: Tolterodine ER 4 mg; alpha blocker (od 4 hr before bedtime) C: Placebo; alpha blocker (od 4 hr before bedtime)	12 wk	I: Age ≥40 yr; 8 micturitions per 24 hr (including 1 urgency episodes per 24 hr with or without urgency); urinary incontinence moderate bladder-related problems despite use of AB ≥1 mo E: PVR ≤200 mL; history of AUR requiring catheterization; poor detrusor function; presumed clinically significant BOO; prostate cancer; PSA ≥10 ng/mL; UTI; neurological disease or injury; antimuscarinic use in prior 30 d	Mean age: 65 Race: 70% white Baseline I-PSS: 18.5
Kaplan, 2009[36] Kaplan, 2013[40] USA N=398	T: Solifenacin 5 mg qd; tamsulosin 0.4 mg qd C: Tamsulosin 0.4 mg qd; placebo	12 wk	I: Age >45 yr; residual OAB symptoms (>8 micturitions and >1 urgency episodes per 24 hr); history of LUTS >3 mo; I-PSS ≥13; PPBC ≥3; PVR ≤200 mL; PFR ≥5 mL/s E: Antimuscarinic therapy or participation in trials involving investigational drug in prior 30 d; urinary or gastric retention; ≥3 recurrent UTI episodes in prior 12 mo; prior or planned prostate surgery; 5-ARIs use with prior 3 mo; PSA >10 ng/mL	Mean age: 65 Race: 84% white Baseline I-PSS: 16.9
MacDiarmid, 2008[37] USA N=420	T: Oxybutynin 10 mg od; tamsulosin 0.4 mg od C: Tamsulosin 0.4 mg od; placebo	12 wk	I: Age ≥45 yr; LUTS (I-PSS ≥13, I-PSS-S ≥8); PFR ≥4 mL/s; void volumes ≥125 mL; PVR ≤200 mL on ≥2 occasions E: History of urinary retention, bladder or prostate cancer, PSA ≥4 ng/mL (unless prostate cancer ruled out), angle-closure glaucoma, prostate surgery, or serious medical comorbidity; current medications for LUTS (α1-blockers other than tamsulosin, or 5α-reductase agents initiated within the past 4 months, and antimuscarinic agents)	Mean age: 63 Race: 90% white Baseline I-PSS: 20.4
Kaplan, 2006[38] Kaplan, 2008[41] Roehrborn, 2008[42] Roehrborn, 2009[43] USA N=879	T: Tolterodine ER 4 mg T_2: Tolterodine ER 4 mg; tamsulosin 0.4 mg C_1: Placebo C_2: Tamsulosin 0.4 mg	12 wk	I: Age ≥40 yr; I-PSS ≥12; I-PSS QoL ≥3; OAB (≥8 voids/24 hr with urgency, ≥3 episodes/24 hr with or without urgency); reported 'some moderate problems' on PPBC E: PVR >200 mL; Qmax <5 mL/s; PSA >10 ng/mL and risk of prostate cancer	Mean age: 62 Race: 81% white Baseline I-PSS: 19.9

AB=alpha blocker; ARI=alpha-reductase inhibitor; AUR=acute urinary retention; bid=twice daily; BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; BPO=benign prostate obstruction; cm^3=cubic centimeters; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; ED=erectile dysfunction; g=grams; HbA1c= glycated haemoglobin; hr=hour; HRQL=health-related quality of life; I=inclusion criteria; IIEF-5=5-item International Index of Erectile Function; I-PSS=International Prostate Symptom Score-Total; I-PSS-S=International Prostate Symptom Score-Storage Subscale; I-PSS-V=International Prostate Symptom Score-Voiding Subscale; LUTS=lower urinary tract symptoms; mg=milligrams; min=minute; mL=milliliters; ng=nanograms; NR=not reported; OAB=overactive bladder; PFR=urine peak flow rate; PPBC=patient perception of bladder condition questionnaire; PPIUS=Patient Perception of Intensity of Urgency Scale; PSA=prostate-specific antigen; PVR=postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; QoL-I=International Prostate Symptom Score-QoL Item; s=second; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

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Table E6. Strength of evidence assessments: tolterodine

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Tolterodine 4 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (419)	WMD = -0.70 [-1.88, 0.48]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	BII, *mean change from baseline*	0							NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (419)	WMD = -0.10 [-0.40, 0.20]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Overall withdrawals	1 (439)	RR 0.84 [0.53, 1.34]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (439)	RR = 0.73 [0.24, 2.27]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	0							NA	Insufficient
Tolterodine, 4 mg plus alpha-blocker vs. placebo	I-PSS/AUA-SI , *mean change from baseline*	1 (416)	WMD=-1.80 [-2.92, -0.68]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	I-PSS QoL, *mean change from baseline*	1 (418)	WMD=-0.40 [-0.66, -0.14]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	AUR	1 (445)	OR=0.65 [0.11, 3.80]	Low	Indirect	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (447)	RR=0.99 [0.64, 1.53]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (447)	RR=2.82 [1.22, 6.53]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
Tolterodine, 4 mg plus alpha-blocker vs. alpha-blocker	Responders	1 (70)	RR = 2.7 [1.55, 4.70]	High	Direct	Precise	Unknown	Undetected[a]	NA	Insufficient
	I-PSS score, *mean change from baseline*	4 (1249)	WMD = -0.19 [-1.08 to 0.69]	Low-Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	I-PSS QoL, mean change from baseline	3 (1182)	WMD= -0.34 [-1.14, 0.46]	Low	Direct	Imprecise	Inconsistent	Undetected[a]	NA	Low
	AUR	3 (1268)	OR= 2.69 [0.25, 28.96]	Low	Indirect	Imprecise	Consistent	Undetected[a]	NA	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	Overall withdrawals	3 (1268)	RR= 1.11 [0.53, 2.34	Low	Direct	Imprecise (CI not centered around 0)	Consistent	Undetected[a]	NA	Low
	Withdrawals due to adverse effects	3 (1268)	RR= 2.17 [0.93, 5.06	Low	Direct	Imprecise (CI skewed towards difference, but not statistically significant)	Consistent	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	1 (652)	RR= 1.26 [1.00, 1.58]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Tolterodine 4 mg vs. alpha-blocker and or 5ARI	I-PSS score, *mean change from baseline*	1 (137)	MD = -2.4 [NR]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	I-PSS QoL, mean change from baseline	1 (137)	MD = -0.1 [NR]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Tolterodine 4 mg vs. tamsulosin 0.4 mg	I-PSS score, *mean change from baseline*	1 (403)	MD = 0.90 [-0.46, 2.26]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	I-PSS QoL, *mean change from baseline*	1(403)	MD = -0.10 [-0.21, 0.41]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Overall withdrawals	1 (432)	RR 0.96 [0.59, 1.55]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (439)	RR = 0.71 [0.23, 2.20]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	0							NA	Insufficient
Tolterodine 4 mg vs. doxazosin 4 mg	I-PSS score, *mean change from baseline*	1 (89)	MD = -0.20 [-2.32, 1.92]	High	Direct	Precise	Unknown	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (89)	MD = -0.20 [-0.61, 0.21]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (202)	RR = 0.83 [0.47, 1.45]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient

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Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	Withdrawals due to adverse effects	1 (202)	RR = 0.65 [0.15, 2.84]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	0							NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible tolterodine trial with a completion date of November 2015. We did not considered the lack of publication bias of this trial an indication of publication bias.

AUR=acute urinary retention; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)*

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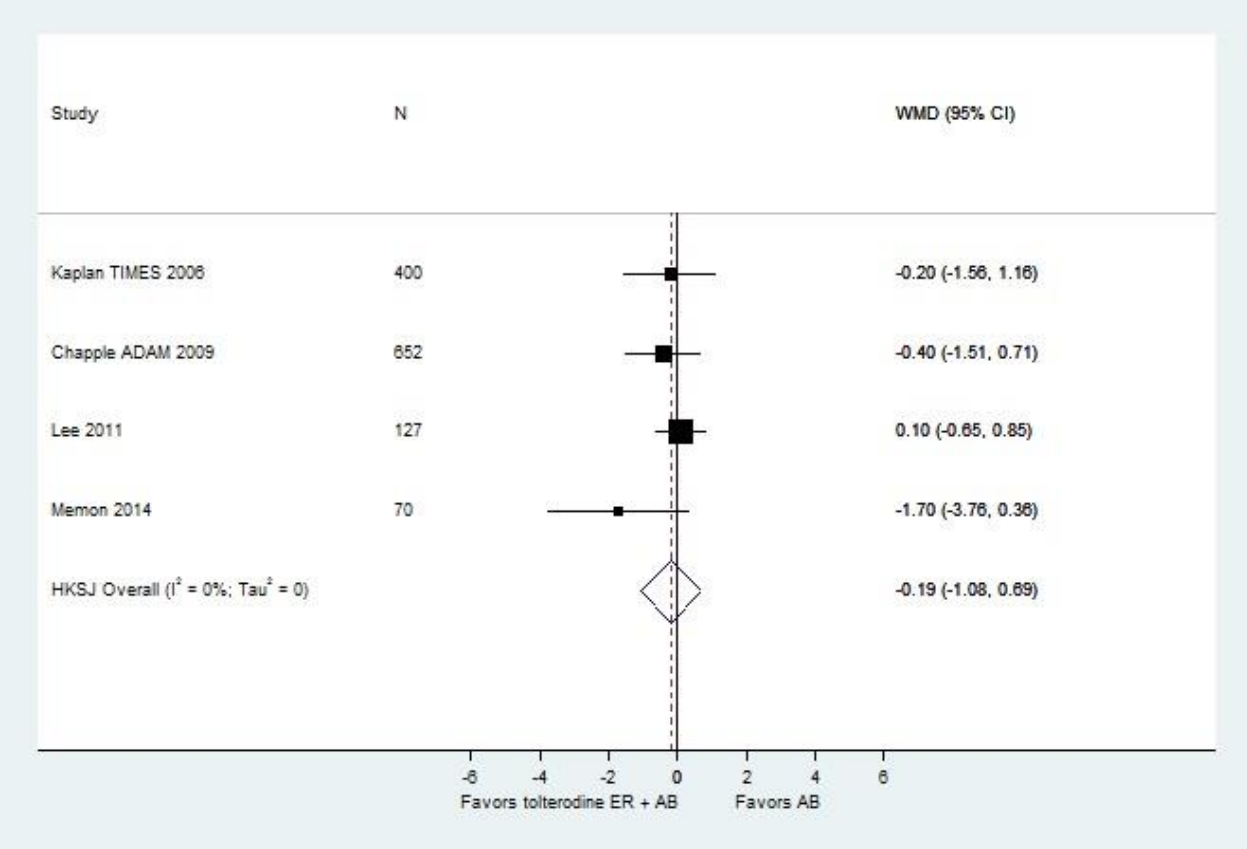
Analyses for Combined Tolterodine + α-Blocker Versus α-Blocker Monotherapy

Figure E1. I-PSS scores, mean change from baseline



* Indicates data was extracted and estimated from graph

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Table E7. Strength of evidence assessments: solifenacin

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Solifenacin 6 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (215)	MD = -0.30 [-1.74, 2.34]	Moderate	Direct	Precise	Unknown	Undetected[a]	NA	Low
	BII, *mean change from baseline*	NR			Direct			Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	NR			Direct			Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (222)	RR = 1.95 [0.64, 5.92]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (222)	RR = 4.97 [0.26, 95.06]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	1 (221)	RR = 1.19 [0.99 to 1.55]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Solifenacin, 3-6 mg plus alpha-blocker vs. placebo	I-PSS/AUA-SI , *mean change from baseline*	3 (1023)	WMD= -1.50 [-1.80 to -1.20]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	I-PSS QoL, *mean change from baseline*	1 (629)	MD= -0.40 [-0.70, -0.10]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Overall withdrawals	3 (1857)	RR= 1.20 [0.46 to 3.13]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	Withdrawals due to adverse effects	3 (1857)	RR= 2.17 [0.72 to 6.55]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	3 (1848)	RR = 1.24 [0.99 to 1.55]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
Solifenacin, 5 or 6 mg plus alpha-blocker vs. alpha-blocker	I-PSS score, mean change from baseline	6 (1948)	WMD=-0.29 [-0.88, 0.30]	Low-Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	I-PSS QoL, *mean change from baseline*	4 (1225)	WMD=-0.18 [-0.39, -0.03]	Low-Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	AUR	4 (2531)	RR=3.75 [0.71, 19.79]	Low-Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Overall withdrawals	7 (3147)	RR=1.02 [0.74, 1.41]	Low-Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Low

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	Withdrawals due to adverse effects	5 (2900)	RR=1.27 [0.81, 2.0]	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	Participants with ≥1 adverse effect	5 (2918)	RR=1.21 [1.09, 1.35]	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate

[a] We searched and screened results from clinicaltrials.gov. We identified for two eligible solifenacin trials; both have been published and included in our review. We did not detect publication bias.

AUR=acute urinary retention; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Analyses for Combined Solifenacin + α-Blocker Versus α-Blocker Monotherapy

Figure E2. I-PSS scores, mean change from baseline (*solifenacin 5-6 mg + tamsulosin 0.2-0.4 mg versus tamsulosin 0.2-0.4 mg*)

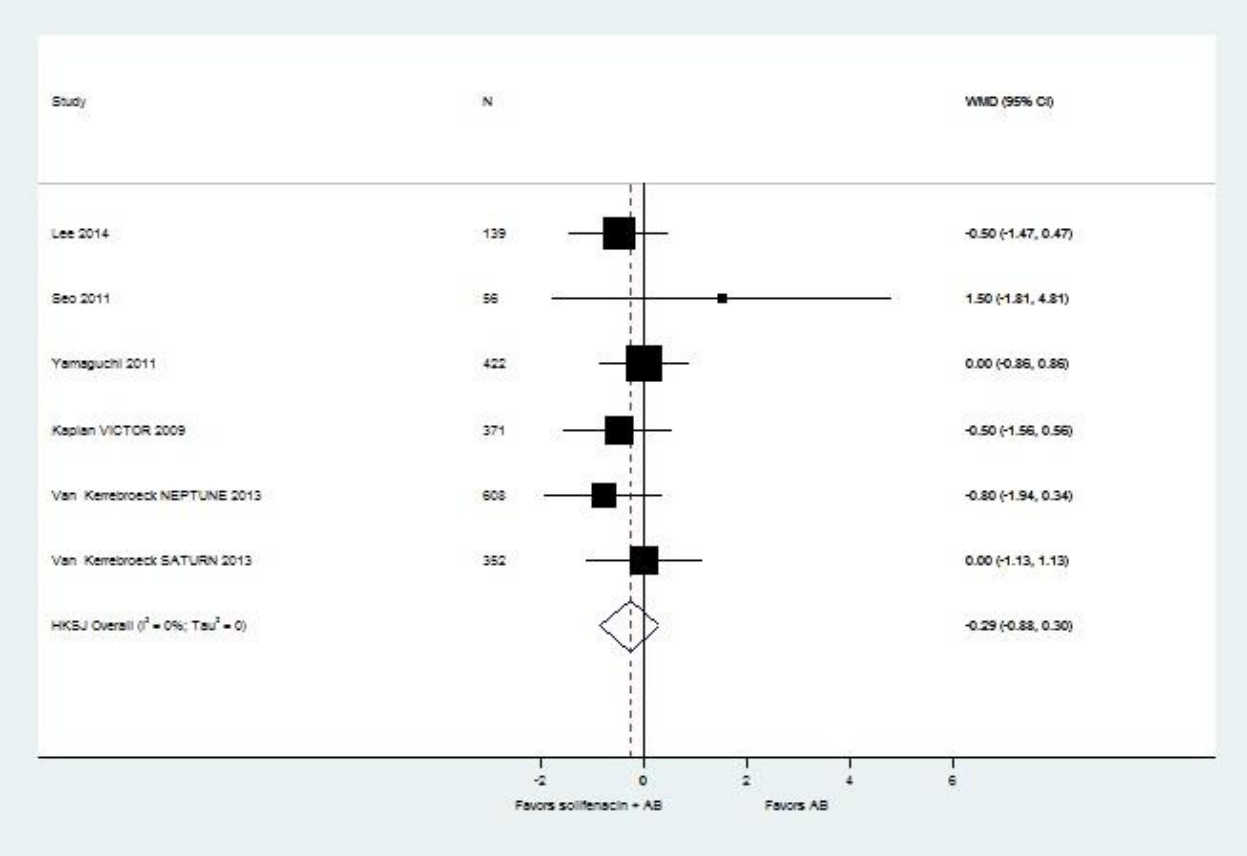

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Figure E3. I-PSS scores, mean change from baseline (solifenacin 5 mg + tamsulosin 0.2 mg vs. tamsulosin 0.2 mg)

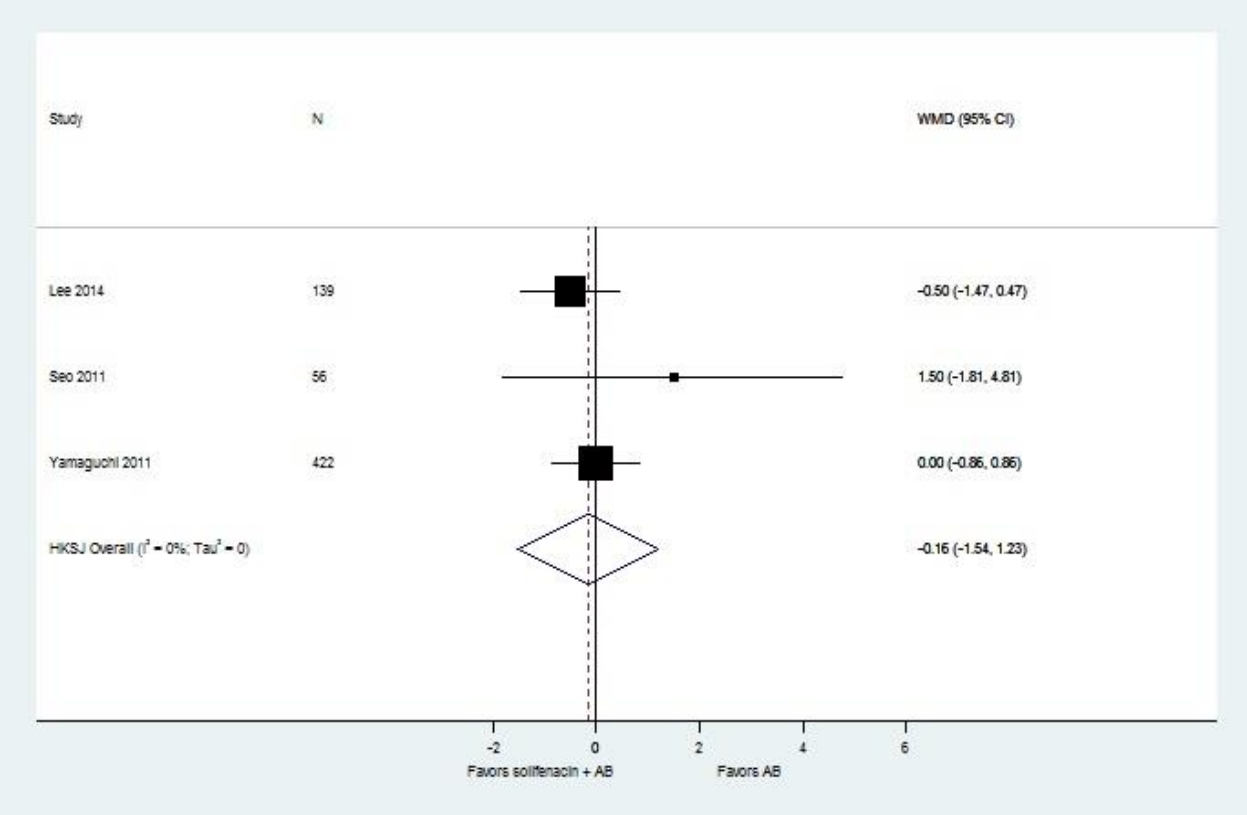

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Figure E4. I-PSS scores, mean change from baseline (solifenacin 5-6 mg + tamsulosin 0.4 mg vs. tamsulosin 0.4 mg)

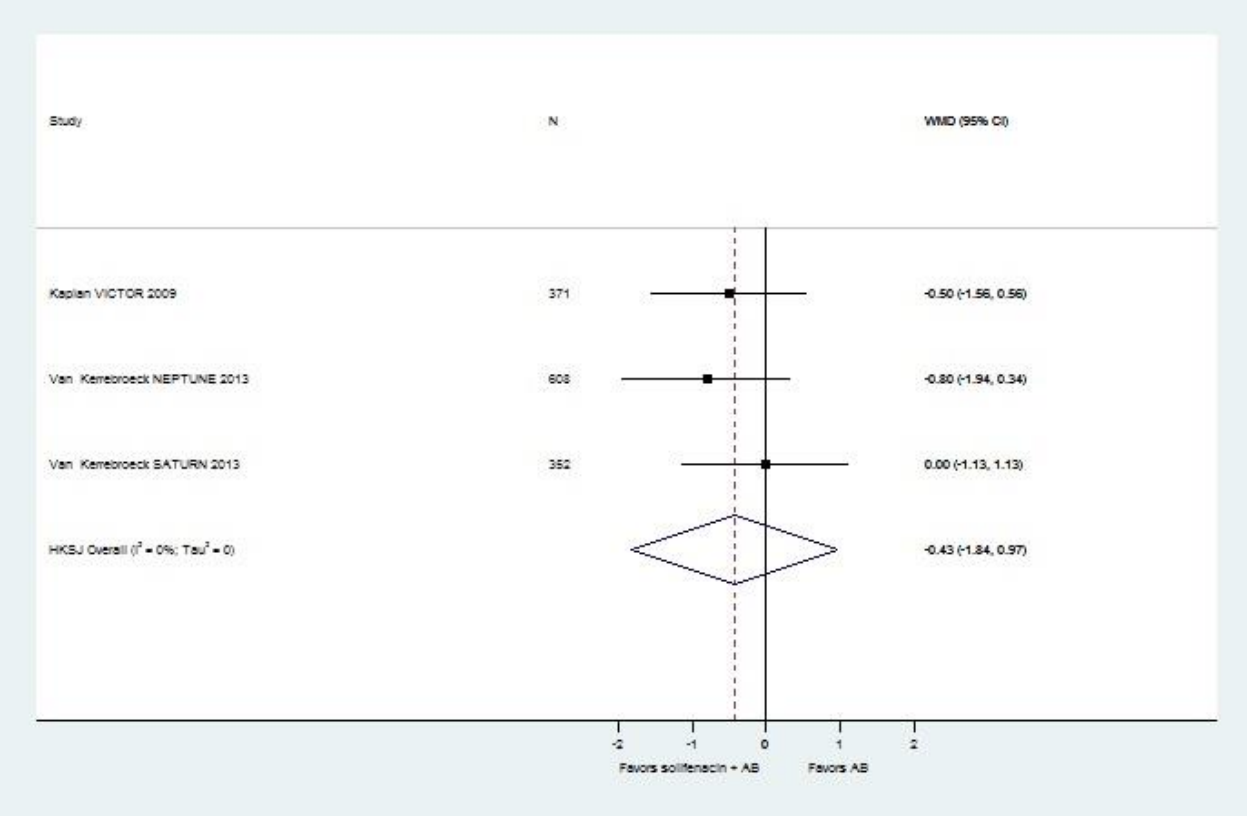

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Table E8. Strength of evidence assessments: fesoterodine

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Fesoterodine 4 mg plus alpha-blocker vs. alpha-blockerAB monotherapy	I-PSS score, mean change from baseline	2 (990)	Konstantinidis, 2013 MD = -1.70 [-5.85, 2.46] Kaplan, 2011 MD = 0.00 [-0.83, 0.83]	ModerateLow	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	AUR	1 (947)	RR 1.00 [0.06 to 15.91]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (947)	RR 1.49 [1.06 to 2.09]	Moderate	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Withdrawals due to adverse effects	1 (947)	RR = 2.30 [1.38 to 3.82]	Moderate	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Participants with ≥1 adverse effect	1 (947)	RR = 1.46 [1.25 to 1.71]	Moderate	Direct	Precise	Unknown	Undetected[a]	NA	Low

[a] We searched and screened results from clinicaltrials.gov. We identified for two eligible solifenacin trials; both have been published and included in our review. We did not detect publication bias.

AUR=acute urinary retention; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Table E9. Strength of evidence assessments: other anticholinergics

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Oxybutynin 10 mg plus tamsulosin 0.4 mg vs. tamsulosin 0.4 mg plus placebo	I-PSS/AUA-SI, *mean change from baseline*	1 (420)	MD = -1.70 [-2.93 to -0.47]	Moderate	Direct	Precise	Unknown	Undetected	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	NR							NA	Insufficient
	AUR	NR							NA	Insufficient
	Overall withdrawals	NR							NA	Insufficient
	Withdrawals due to adverse effects	1 (420)	RR = 1.06 [0.60 to 1.90]	Moderate	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	Participants with ≥1 adverse effect	1 (420)	RR = 1.00 [0.80 to 1.25]	Moderate	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
Trospium 45 mg plus terazosin 5 mg (alpha-blocker) vs. placebo plus terazosin 5 mg	I-PSS/AUA-SI, *mean change from baseline*	1 (58)	Unable to determine MD	Moderate	Direct	Unclear	Unknown	Undetected	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	NR							NA	Insufficient
	AUR	NR							NA	Insufficient
	Overall withdrawals	NR							NA	Insufficient
	Withdrawals due to adverse effects	NR							NA	Insufficient
	Participants with ≥1 adverse effect	1 (58)	RR = 1.47 [0.56 to 3.88]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Darifenacin 7.5 mg plus doxazosin 4 mg (alpha-blocker) vs. doxazosin 4 mg	I-PSS/AUA-SI, *mean change from baseline*	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 MD = -2.6 [NR] Ceylan, 2012 MD = -3.47 [NR]	Low-Moderate	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 MD NR Ceylan, 2012 MD = -0.8 [NR]	Low-Moderate	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	AUR	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 RR = 4.00 [0.47 to 33.73] Ceylan, 2012 NR	Low-Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	Overall withdrawals	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 RR not calculable Ceylan, 2012 RR = 0.98 [0.020 to 48.50]	Low-Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	Singh, 2015 (60) Ceylan, 2012 (101)	Singh, 2015 RR = 9.00 [0.51 to 160.18] Ceylan, 2012 RR = 0.98 [0.020 to 48.50]	Low-Moderate	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified no eligible trials and detected no publication bias.

AUR=acute urinary retention; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Appendix F. Supporting Tables: Mirabegron

Table F1. Risk of bias assessments: mirabegron trials

Study	Overall Risk of Bias Assessment	Rationale
Ichihara, 2015[44]	High	Open label, outcome blinding not described, moderate attrition
Nitti, 2013[45]	Low	

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Table F2. Characteristics of BPH treatment, comparison, and population: mirabegron trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Ichihara, 2015[44] Japan N=94	T: Mirabegron 50 mg qd; tamsulosin 0.2 mg qd C: Tamsulosin 0.2mg qd	8 wk	I: Persistent OAB symptoms after tamsulosin 0.2 mg qd ≥8 wk; OABSS ≥3; urinary urgency ≥1 per wk E: PVR >100 mL; Qmax <5 mL/s; history of urinary retention neurogenic bladder, clean intermittent catheterization, severe bladder diverticulum, or urethral stricture; planning to have a child; suspected malignant disease; previous intrapelvic irradiation; suspected UTI; renal or hepatic impairment; taking medicine contraindicated to combination with mirabegron	Mean age: 75 Race: NR Baseline I-PSS: 13.5
Nitti, 2013[45] USA and Canada N=200	T_1: Mirabegron 100 mg qd T_2: Mirabegron 50 mg qd C: Placebo	12 wk	I: Age >45 yr; voiding/LUTS ≥3 mo; I-PSS ≥8; BOOI ≥20; Qmax ≤12 mL/s; voided volume ≥120 mL during free flow E: History of urinary retention in prior 12 mo; history of carcinoma, prostate cancer, pelvic radiation therapy in prior 5 yr; neurogenic bladder; UTI or recurrent UTIs; previous or planned prostate surgery or other invasive procedures (excluding prostate biopsy) within 12 mo; chronic inflammation such as chronic prostatitis; stone in bladder or ureter; other causes of BOO such as bladder neck stenosis or urethral stricture	Mean age: 63 Race: 54% white Baseline I-PSS: 19.9

BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; C=comparator group; E=exclusion criteria; I=inclusion criteria; I-PSS=International Prostate Symptom Score; LUTS=lower urinary tract symptoms; mg=milligrams; mL=milliliters; NR=not reported; OAB=overactive bladder; OABSS=overactive bladder symptoms score; PVR= postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; s=second; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

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Table F3. Strength of evidence assessments: mirabegron

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Mirabegron 50 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (135)	MD = -5.7 [NR]	Low	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	AUR	1 (135)	RR = 0 [0.01, 7.47]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (135)	RR = 1.39 [0.24, 8.07]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (135)	RR = 0.93 [0.13, 6.40]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Mirabegron 100 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (130)	MD = -4.3 [NR]	Low	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	AUR	1 (130)	RR = 1 [0.06, 15.65]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (130)	RR = 3.5 [0.76, 16.22]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (130)	RR = 1 [0.15, 6.89]	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Mirabegron 50 mg qd plus alpha-blocker vs. alpha-blocker	I-PSS/AUA-SI, *mean change from baseline*	1 (94)	MD = 2.08 [NR]	High	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (94)	MD = -0.71 [NR]	High	Direct	Unknown	Unknown	Undetected[a]	NA	Insufficient
	AUR	1 (94)	RR = 2.66 [0.11, 63.40]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (94)	RR = 9.75 [0.56, 170.43]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (94)	RR = 9.75 [0.56, 170.73]	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial that has not yet been completed. We detected no publication bias.

AUR=acute urinary retention; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Appendix G. Supporting Tables and Figures: PDE-5 Inhibitors

Table G1. Risk of bias assessments: PDE-5 trials

Study	Overall Risk of Bias Assessment	Rationale
Casabe, 2014[46]	Low	
Kumar, 2014[47]	High	Randomization methods not reported, different pills taken at different times, inadequate patient and provider blinding; assessors likely unblinded, no attrition
Singh, 2014[39]	High	Allocation methods unclear, open label
Takeda, 2014[48]	Low	Randomization and allocation methods unclear.
Abolyosr, 2013[49]	High	Randomization and allocation methods unclear, unblinded and no placebo, no between group analyses, attrition unclear
Regadas, 2013[50]	Moderate	Allocation methods unclear, small sample size, attrition unclear
Yokoyama, 2013[51]	Moderate	Allocation methods unclear, baseline reported with standard deviation but results reported with standard error
Egerdie, 2012[52]	Low	
Gacci, 2012[53]	Moderate	
Goldfischer, 2012[54]	Low	
Madani, 2012[55]	Moderate	Allocation methods unclear, “standard therapy” differed between treatment groups, no between group analyses, no attrition
Oelke, 2012[56]	Low	
Ozturk, 2012[57]	High	Allocation methods unclear, unblinded and no placebo, moderate sample size, some results not reported
Takeda, 2012[58]	Low	
Kim, 2011[59]	Moderate	Allocation methods unclear. groups similar at baseline except for history of erectile dysfunction, pilot study, baseline reported with standard deviation but results reported with standard error
Porst, 2011[60]	Low	
Dmochowski, 2010[61]	Moderate	Completer analysis
Tuncel, 2010[62]	Moderate	Randomization methods not reported, unblinded and no placebo, small sample size, some key outcomes reported in figures only
Liguori, 2009[63]	High	Allocation methods unclear, open label, no between group analyses, completer analysis
Roehrborn, 2008[64]	Low	
Stief, 2008[65]	Low	
McVary, 2007a[66]	Low	
McVary, 2007b[67]	Moderate	Allocation methods unclear, one-sided alpha level used, unclear how attrition handled
Kaplan, 2007[68]	High	Randomization and allocation methods unclear, unblinded and no placebo, small sample size

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Table G2. Summary of PDE-5 Trials: Tadalafil

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total randomized	5786 (40 to 1058)	15
Percentage randomized based on # screened	70 (54 to 87)	13
Received placebo, # randomized (% all randomized)	1641 (28) (51 to 304)	10
Received alpha-blocker, #randomized (% all randomized)	481 (8) (20 to 168)	7
Received combined tadalafil and alpha-blocker, # randomized (% all randomized)	112 (2) (20 to 44)	4
Received 5-ARI, # randomized (% all randomized)	350 (6)	1
Received combined tadalafil and 5-ARI, # randomized (% all randomized)	346 (6)	1
Age of subjects, years	62 (59 to 65)	14
Percentage white race	55 (0[a] to 93)	13
Baseline I-PSS	18 (15 to 22)	15
Percentage with over active bladder symptoms	1- 7%[b]	2
Percentage with erectile dysfunction	72 (59 to 100)	9[c]

[a] All subjects from trials conducted in Asia (Korea, Japan, India: k=6; n=2003) presumed to be non-European white
[b] Reported as previously received OAB therapy
[c] One trial did not report percentage with ED but change in the Index of Erectile Function score was an outcome; Another trial only reported report percentage with ED in men who were sexually active.

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Table G3. Characteristics of BPH treatment, comparison, and population: PDE-5 trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Casabe, 2014[46] North America, South America, Europe N=696	T: Tadalafil 5 mg qd; finasteride 5 mg qd C: Finasteride qd	12 wk	I: Age >45 yr; I-PSS ≥13; LUTS/BPH >6 mo; prostate volume ≥30 mL; Qmax 5-15 mL/s; naïve to 5-ARIs E: NR	Mean age: 64 Race: 86% white Baseline I-PSS: 17.3
Kumar, 2014[47] India N=75	T_1: Tadalafil 10 mg qd; afluzosin 10 mg qd T_2: Tadalafil 10 mg qd C_1: Afluzosin 10 mg qd	12 wk	I: Age >50 yr; I-PSS ≥8 E: According to the specified contraindications of both the drugs	Mean age: 62 Race: NR Baseline I-PSS: 17.8
Singh, 2014[39] India N=133	T_1: Tadalafil 10 mg qd; tamsulosin 0.4 mg qd T_2: Tadalafil 10 mg qd C: Tamsulosin 0.4 mg qd	13 wk	I: Age >45 yr; I-PSS ≥8; LUTS/BPH ≥6 mo; PSA ≤4.0 ng/mL; Qmax 5-15 mL/s; voided volume >125 mL E: Contraindications to drugs in study; use of finasteride/dutasteride or prohibited medications like alpha agonists; syncope, orthostatic hypotension; BOO due to cancer, calculi or stricture; previous TURP; any neurological disorders affecting storage and voiding; prostatitis or cancer; recent AUR; UTI; poorly controlled diabetes mellitus or hypertension	Mean age: 61 Race: NR Baseline I-PSS: 21.0
Takeda, 2014[48] Lee, 2014[69] Japan, Korea N=610	T: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; Qmax 4-15 mL/s; prostate volume >20 mL; PVR <300 mL E: PSA >10 ng/mL (or ≥4 ng/mL if prostate cancer could not be ruled out); sugary on pelvic urinary tract; recent finasteride, dutasteride, anti-androgenic hormone therapy, or other BPH, ED or OAB therapies	Mean age: 61 Race: NR Baseline I-PSS: 18.7
Abolyosr, 2013[49] Egypt N=150	T_1: Sildenafil 50 mg; doxazosin 2 mg T_2: Sildenafil 50 mg C: Doxazosin 2 mg	17 wk	I: Age ≥45 yr; I-PSS >7; LUTS/ BPH ≥3; ED ≥3 mo; IIEF-EF <25 E: Previous prostatic surgery or other surgery for BPH; cystitis or bladder stones; PSA >10; contraindications for medical treatment for ED (cardiac problems which contraindicate the use of PDE-5 inhibitors, needing surgery); previous unresponsiveness to PDE‑5s	Mean age: NR Race: NR Baseline I-PSS: 16.7
Regadas, 2013[50] Brazil N= 40	T: Tadalafi 5 mg qd; tamsulosin 0.4 mg qd C: Placebo; tamsulosin 0.4 mg qd	4 wk	I: Age ≥45 yr; I-PSS >14; LUTS secondary to BPH; BOOI >20 E: Prostate cancer, LUTS not related to BPH, hypotension, retinitis pigmentosa; recent 5-ARIs, ABs, anticholinergics, PDE-5s; surgery of the prostate, urethra, or bladder; neurological disease, urinary retention, bladder stones; use of nitrates; cardiovascular, hepatic, or renal insufficiency	Mean age: 61 Race: NR Baseline I-PSS: 20.5

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Yokoyama, 2013[51] Lee, 2014[69] Japan, Korea, Taiwan N=1224	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C_1: Placebo C_2: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥45 yr; I-PSS ≥13; Qmax 4 - 15 mL/s; prostate volume ≥20 mL; LUTS >6 mo; PVR <300 mL E: PSA >10 ng/mL (or PSA 4 - 10 ng/mL, unless clinically negative for prostate cancer); history of symptomatic orthostatic hypotension, dizziness, vertigo, LOC, or syncope; clinical prostate cancer or urinary tract conditions affecting LUTS; severe renal or hepatic insufficiency; recent finasteride or dutasteride; cardiac conditions or nitrate use	Mean age: 63 Race: NR Baseline I-PSS: 16.8
Egerdie, 2012[52] Roehrborn, 2014[70] Porst, 2013[71] Porst, 2013[72] Brock, 2014[73] Oelke, 2014[74] Europe, Mexico, USA N=806	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; LUTS >6 mo and ED ≥3 mo; Qmax 4-15 mL/s; ≥4 intercourse attempts; 70% compliant during run-in; PVR <300 mL E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless cancer ruled out); ED due to other primary sexual disorders or endocrine disease; prior nonresponsiveness to PDE 5s; certain cardiac conditions; recent finasteride or dutasteride; recent lower urinary tract instrumentation; urethral or intravesicle obstruction; recent urinary retention or stones; neurogenic bladder, renal insufficiency, or hepatic impairment	Mean age: 63 Race: 93% white Baseline I-PSS: 18.3
Gacci, 2012[53] Italy N=60	T: Vardenafil 10 mg qd; tamsulosin 0.4 mg qd C: Placebo; tamsulosin 0.4 mg qd	12 wk	I: Age 40–80 yr; LUTS (I-PSS ≥12, OAB questionnaire-Short Form ≥8); voided volume <400 mL; Qmax >5 mL/s (with a voided volume >150 mL) E: Hypersensitivity to vardenafil or tamsulosin; drugs incompatible with vardenafil or tamsulosin; bladder failure (abnormal urodynamic assessment in men with PVR >250 mL); neurogenic bladder (multiple sclerosis, Parkinson, spinal cord injury), UTI, LUT disease/treatment (urethral stenosis, 5-ARI, or BPH surgery); severe systemic disease (hepatic, cardiac, hematological, or neoplastic); unable to complete the protocol	Mean age: 68 Race: 100% white Baseline I-PSS: 19.6
Goldfischer, 2012[54] USA N= 318	T: Tadalafil 5 mg qd; AB C: Placebo; AB	12 wk	I: Age ≥45 yr; LUTS from BPH >6 mo; stable dose of AB for BPH ≥4 wk E: PSA >10 ng/mL (or PSA ≥4 to <10 ng/mL, unless malignancy ruled out; PVR ≥300 mL; AB for hypertension	Mean age: 67 Race: 89% white Baseline I-PSS: 13.6
Madani, 2012[55] Iran N=132	T: Tadalafil 10 mg qd; standard treatment (AB or finasteride) C: Placebo; standard treatment (AB or finasteride)	13 wk	I: I-PSS ≥8; LUTS/BPH; Qmax 5-15 mL/s; no indication for surgical intervention; had reached plateau levels of response to standard treatment E: History of refractory urinary retention, persistent gross hematuria, recurrent UTI renal insufficiency, bilateral hydronephrosis or bladder stones due to BPH; spinal cord injury, prostatitis, bladder or prostate malignancy, bladder neck or urethral stricture, PVR >120; pelvic trauma	Mean age: 65 Race: NR Baseline I-PSS: 13.4

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
			or surgery; recent myocardial infarction, unstable angina; use of nitrates or nitric oxide donors, androgens or anti-androgens, anticoagulants, cytochrome p-450 3A4 inhibitors	
Oelke, 2012[56] Oelke, 2014[75] Roehrborn, 2014[70] Porst, 2013[71] Porst, 2013[72] Brock, 2013[76] Brock, 2014[73] Oelke, 2014[74] Europe, Mexico, Australia N=682	T: Tadalafil 5 mg qd C_1: Placebo C_2: Tamsulosin 0.4 mg qd	12 wk	I: Age ≥45 yr; I-PSS ≥13; history of LUTS secondary to BPH for >6 mo; Qmax 4 - 15 mL/s; compliance during run-in ≥70% E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recent finasteride or dutasteride, recent lower urinary tract instrumentation or stones, or urinary retention; history of urethral or bladder neck obstruction; neurogenic bladder; creatinine clearance <30 mL/min; severe hepatic impairment; certain cardiovascular conditions; current nitrate therapy; planned cataract surgery; symptomatic orthostatic hypotension, recurrent dizziness, vertigo, loss of consciousness, syncope	Mean age: 64 Race: 77% white Baseline I-PSS: 17.1
Ozturk, 2012[57] Turkey N=100	T: Sildenafil 50 mg; alfuzosin XL 10 mg C: Alfuzosin XL 10 mg	13 wk	I: Age >45 yr; I-PSS ≥12, QoL ≥3; moderate-to-severe LUTS; naïve to treatment for LUTS or ED E: Contraindications to alfuzosin or sildenafil; bladder stones or previous prostatic operations; history of AUR; urethral strictures, PVR >200 mL; prostate cancer, chronic renal or liver insufficiency	Mean age: NR Race: NR Baseline I-PSS: 19.9
Takeda, 2012[58] Japan N=562	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; Qmax 4 - 15 mL/s; prostate volume >20 mL; PVR <300 mL E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless clinically negative for prostate cancer); sugary on pelvic urinary tract; clinical prostate cancer or urinary tract conditions affecting LUTS; renal insufficiency; recent dutasteride	Mean age: 67 Race: NR Baseline I-PSS: 16.4
Kim, 2011[59] Lee, 2014[69] Korea N= 202	T: Tadalafil 5 mg qd C_1: Tamsulosin 0.2 mg qd C_2: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; Qmax 4-15 mL/s; LUTS >6 mo; PVR ≤300 mL E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); history of symptomatic orthostatic hypotension, dizziness, vertigo, LOC, or syncope; recent finasteride or dutasteride; other BPH, ED or OAB therapies	Mean age: 62 Race: NR Baseline I-PSS: 17.4
Porst, 2011[60] Roehrborn, 2014[70] Porst, 2013[71] Porst, 2013[72] Brock, 2013[76]	T: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; history of LUTS secondary to BPH for >6 mo; Qmax 4 - 15 mL/s; PVR ≤300 mL; compliance during run-in ≥70% E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recent finasteride or dutasteride, recent lower urinary tract instrumentation or stones, or urinary retention; history of urethral or bladder neck	Mean age: 65 Race: 92% white Baseline I-PSS: 16.8

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Brock, 2014[73] Oelke, 2014[74] Argentina, Germany, Italy, Mexico, US N=325			obstruction; neurogenic bladder; creatinine clearance <30 mL/min; severe hepatic impairment; certain cardiovascular conditions; current nitrate therapy	
Dmochowski, 2010[61] Dmochowski, 2013[77] USA, Canada N=200	T: Tadalafil 20 mg qd C: Placebo	12 wk	I: Age ≥40 yr; I-PSS ≥13; LUTS >6 mo; PVR <350 mL E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recent 5-ARIs; penile or pelvic surgery, radiotherapy, malignancy, trauma, instrumentation; urinary retention or stones; urethral obstruction; atonic, decompensated or hypocontractile bladder; detrusor-sphincter dyssynergia; intravesical obstruction; urinary tract inflammation or infection	Mean age: 59 Race: 77% white Baseline I-PSS: 21.7
Tuncel, 2010[62] Turkey N= 60	T_1: Sildenafil 25 mg qd 4d/wk; tamsulosin 0.4 mg qd T_2: Sildenafil 25 mg qd 4 d/wk C: Tamsulosin 0.4 mg qd	8 wk	I: I-PSS ≥12; SHIM ≤20; BPH/LUTS and ED E: Drugs or surgery for BPH or ED, recent prostate biopsy or 5-ARIs; any urologic cancer, prostate or bladder/pelvic radiation or surgery, urinary stone, active UTI, recent AUR; recent urethral catheter; acute or chronic hepatic failure, renal dysfunction; poorly controlled diabetes, nitrates use	Mean age: NR Race: NR Baseline I-PSS: 15.3
Liguori, 2009[63] Italy N=66	T_1: Tadalafil 20 mg every other day; alfuzosin extended release 10 mg qd T_2: Tadalafil 20 mg qd C: Alfuzosin extended release 10 mg qd	12 wk	I: Age 50–75 yr; I-PSS >8; LUTS/BPH ≥6 mo; untreated ED of any grade E: Contraindications of either drug; medications to control bladder symptoms; bladder tumors, urethral strictures, neurogenic bladder dysfunction, prostatitis, prostate cancer, PSA >20 ng/mL; prostate surgery or radiotherapy, AUR or indwelling catheter; acute UTI; ever used 5-ARIs, ABs, or PDE-5s	Mean age: 62 Race: NR Baseline I-PSS: 14.9
Roehrborn, 2008[64] Broderick, 2010[78] Roehrborn, 2014[70] Porst, 2013[71] Porst, 2013[72] Brock, 2013[76] Brock, 2014[73] Oelke, 2014[74] 10 countries N=1689	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd T_3: Tadalafil 20 mg qd C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥13; history of LUTS secondary to BPH for ≥6 mo; Qmax 4 - 15 mL/s; PVR ≤300 mL E: PSA >10 ng/mL (PSA 4 - 10 ng/mL, unless negative biopsy); recent finasteride or dutasteride, antiandrogens, or potent cytochrome P450 3A4 inhibitor; penile or pelvic problems other than LUTS/BPH; clinically significant renal, hepatic, cardiovascular, or diabetic disease; spinal cord injury, cancer chemotherapy	Mean age: 62 Race: 85% white Baseline I-PSS: 17.3
Stief, 2008[65] Germany	T: Vardenafil 10 mg bid C: Placebo	8 wk	I: Age 45–64 yr; I-PSS ≥12; LUTS ≥6 mo	Mean age: 56 Race: 99% white

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
N=222			E: Contraindications to vardenafil; spinal cord injury; prostatitis; history of prostate or bladder cancer; bladder or urethra stricture; PVR ≥100 mL; pelvic trauma or surgery; any malignancies; life expectancy of <3 yr; use of nitrates or nitric oxide donors, androgens or anti-androgens, anticoagulants, cytochrome P-450 3A4 inhibitors, alpha1-blockers, or any treatment for ED	Baseline I-PSS: 16.8
McVary, 2007a[66] McVary, 2008[79] USA N=370	T: Sildenafil 50-100 mg C: Placebo	12 wk	I: Age ≥45 yr; I-PSS ≥12; IIEF-EF ≤25 E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless clinically negative for prostate cancer), prostate cancer, prostate/bladder/pelvic radiation or surgery; causes of symptoms other than BPH (urinary tract disease, recent cystoscopy, urinary calculi, AUR, recurrent UTIs, recent catheterization for outflow obstruction); hypotension, hypertension, orthostatic hypotension, or significant cardiovascular disease; hepatic or renal disease, poorly-controlled diabetes, retinitis pigmentosa; use of nitrates, antimuscarinics, recent 5-ARIs, recent ABs	Mean age: 60 Race: 82% white Baseline I-PSS: NR
McVary, 2007b[67] USA N= 543	T_1: Tadalafil 5 mg T_2: Tadalafil 20 mg C: Placebo	6 wk	I: Age ≥45 yr; LUTS/BPH ≥6 mo; agreed not to use other BPH meds E: PSA >10 ng/mL (PSA 4 - 10 ng/mL, unless negative biopsy); recent finasteride or dutasteride; radical prostatectomy or other pelvic surgery; neurological condition affecting bladder function; recent lower urinary tract instrumentation, retention or stones; past urethral obstruction; detrusor-sphincter dyssynergia; UTI or urinary tract inflammation; intravesical obstruction due to the prostate median lobe; prostate cancer; PVR ≥ 200 mL at visit 2; certain cardiovascular diseases, clinically significant renal or hepatic insufficiency, recent stroke or spinal cord injury; current nitrates, cancer chemotherapy, antiandrogens or a potent cytochrome P450 3A4 inhibitor; or HbA1c >9%	Mean age: 62 Race: 81% white Baseline I-PSS: 17.9
Kaplan, 2007[68] USA N= 124	T_1: Sildenafil 25 mg qd; alfuzosin 10 mg qd T_2: Sildenafil 25 mg qd C: Alfuzosin 10 mg qd	12 wk	I: Age 50-76 yr; moderate to severe untreated LUTS and self-reported ED E: NR	Mean age: 64 Race: NR Baseline I-PSS: 17.3

AB=alpha blocker; ARI=alpha-reductase inhibitor; AUR=acute urinary retention; bid=twice daily; BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; ED=erectile dysfunction; HbA1c= glycated haemoglobin; HRQL=health-related quality of life; I=inclusion criteria; IIEF-EF=international index of erectile function questionnaire-erectile function subscale; I-PSS=International Prostate Symptom Score; LOC=loss of consciousness; LUTS=lower urinary tract symptoms; mg=milligrams; min=minute; mL=milliliters; ng=nanograms; NR=not reported; OAB=overactive bladder; PDE-5=phosphodiesterase-5 inhibitors; prn=as needed; PSA=prostate-specific antigen; PVR= postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; s=seconds; SHIM=sexual health inventory for men; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; TURP=transurethral resection of the prostate; UTI=urinary tract infection; wk=weeks; yr=years

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Table G4. Strength of evidence assessments: tadalafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Tadalafil 5 mg vs. placebo	I-PSS/AUA-SI, *mean change from baseline*	9 (3024)	WMD = -1.79 [-2.29 to -1.29]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Moderate
	Responders – change from baseline of ≥3 points in I-PSS scores	1 (281)	RR = 1.36 [1.03 to 1.78]	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	BII, *mean change from baseline*	7 (2161)	WMD = -0.52 [-0.78 to -0.26]	Low	Direct	Imprecise	Consistent	Undetected[a]	NA	Moderate
	I-PSS QoL, mean change from baseline	8 (2605)	WMD = -0.27 27 [-0.31 to -0.23]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	Overall withdrawals	9 (3082)	RR = 1.00 [0.77 to 1.3]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	Withdrawals due to adverse effects	9 (3082)	RR = 1.80 [1.03 to 3.44]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
	Participants with ≥1 adverse effect	9 (3082)	RR = 1.25 [1.09 to 1.44]	Low	Direct	Precise	Consistent	Undetected[a]	NA	High
Combined tadalafil 5-20 mg with any alpha-blocker vs. any alpha-blocker	I-PSS/AUA-SI, mean change from baseline	4 (214)	WMD = -2.01 [-4.03 to -0.00]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	I-PSS QoL, mean change from baseline	3 (174)	WMD = -0.44 [-0.73 to -0.15]	High	Direct	Precise	Consistent	Undetected[a]	Confounding	Low (Clinically Equivalent)
	Overall withdrawals	4 (224)	RR = 0.80 [0.12 to 5.29]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	4 (224)	RR = 1.13 [0.12 to 11.03]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	NR							NA	Insufficient
Tadalafil 5 mg vs. tamsulosin 0.2-0.4 mg	I-PSS/AUA-SI, *mean change from baseline*	3 (742)	WMD = 0.07 07 [-2.12 to 2.23]	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	BII, *mean change from baseline*	3 (731)	WMD = -0.02 [-1.52 to 1.48]	Moderate	Direct	Imprecise	Inconsistent	Undetected[a]	NA	Low
	I-PSS QoL, *mean*	3	WMD = -0.01	Moderate	Direct	Precise	Inconsistent	Undetected[a]	NA	Low

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	change from baseline	(742)	[-0.75 to 0.73]							
	Overall withdrawals	3 (742)	RR = 1.35 (0.30 to 6.05)	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	Withdrawals due to adverse effects	3 (742)	RR = 2.68 (1.09 to 6.60)	Moderate	Direct	Precise	Consistent	Undetected[a]	NA	Moderate
	Participants with ≥1 adverse effect	3 (742)	RR = 0.99 (0.38 to 2.54)	Moderate	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
Tadalafil 10-20 mg vs. alfuzosin 10 mg	I-PSS/AUA-SI, *mean change from baseline*	2 (87)	Kumar, 2014 MD = 3.20 [1.71, 4.69] Liguori, 2009 MD = 3.90 [0.72, 7.08]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	I-PSS QoL, *mean change from baseline*	2 (87)	Kumar, 2014 MD = 0.80 [0.35, 1.25] Liguori, 2009 MD = 0.30 [-0.35, 0.95]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Low
	Overall withdrawals	2 (93)	Kumar, 2014 RR not estimable Liquori, 2009 RR = 0.52 [0.11, 2.56]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	2 (93)	Kumar, 2014 RR not estimable Liquori, 2009 RR = 0.35 [0.04, 3.10]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	NR							NA	Insufficient
Tadalafil 5 mg & finasteride 5 mg vs. Placebo & finasteride 5 mg	I-PSS/AUA-SI, mean change from baseline	1 (696)	MD = -1.0 (-1.9 to -0.2)	Low	Direct	Precise	Unknown	Undetected	NA	Low
	I-PSS QoL, *mean change from baseline*	1 (696)	MD = -0.2 (-0.4 to 0.0)	Low	Direct	Precise	Unknown	Undetected	NA	Low
	Overall withdrawals	1 (696)	RR = 0.63 [0.44, 0.91]	Low	Direct	Precise	Unknown	Undetected	NA	Low
	Withdrawals due to adverse effects	1 (696)	RR = 1.50 [0.44, 5.06]	Low	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	Participants with ≥1 adverse effect	1 (696)	RR = 1.15 [0.91, 1.45]	Low	Direct	Imprecise	Unknown	Undetected	NA	Insufficient

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Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Tadalafil 10 mg & AB OR finasteride vs. Placebo & AB OR finasteride	I-PSS/AUA-SI, mean change from baseline	1 (132)	MD = -3.1 (-4.5 to -1.7)	Moderate	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (132)	MD = -0.6 (-0.9 to -0.3)	Moderate	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
	Withdrawals due to adverse effects	1 (132)	RR = 1.50 [0.44, 5.07]	Moderate	Direct	Imprecise	Unknown	Undetected	NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified 14 eligible trials; 12 had been published and included in our review. The two that are not yet published have only recently completed. We detected no publication bias.

AUR=acute urinary retention; BII = BPH Impact Index; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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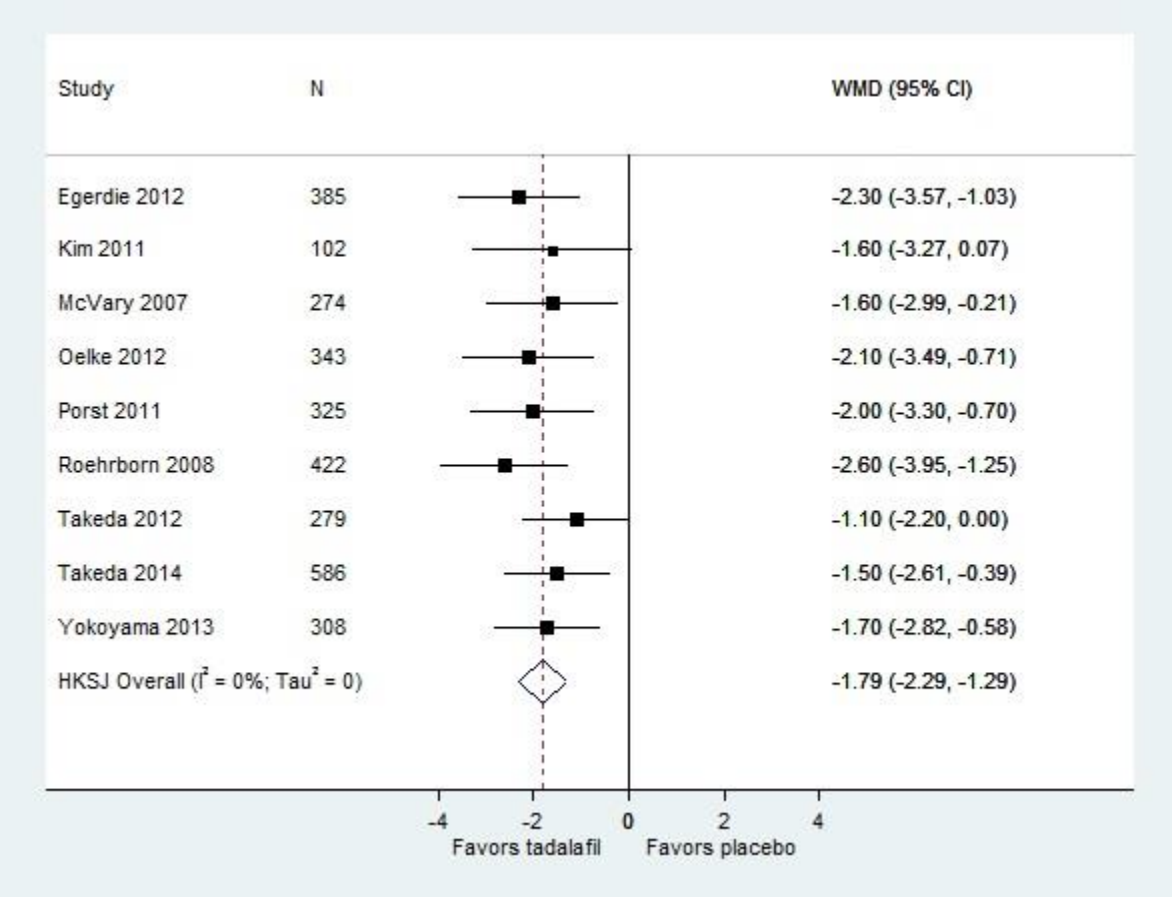
Efficacy of Tadalafil

Figure G1. I-PSS scores, mean change from baseline: tadalafil vs. placebo



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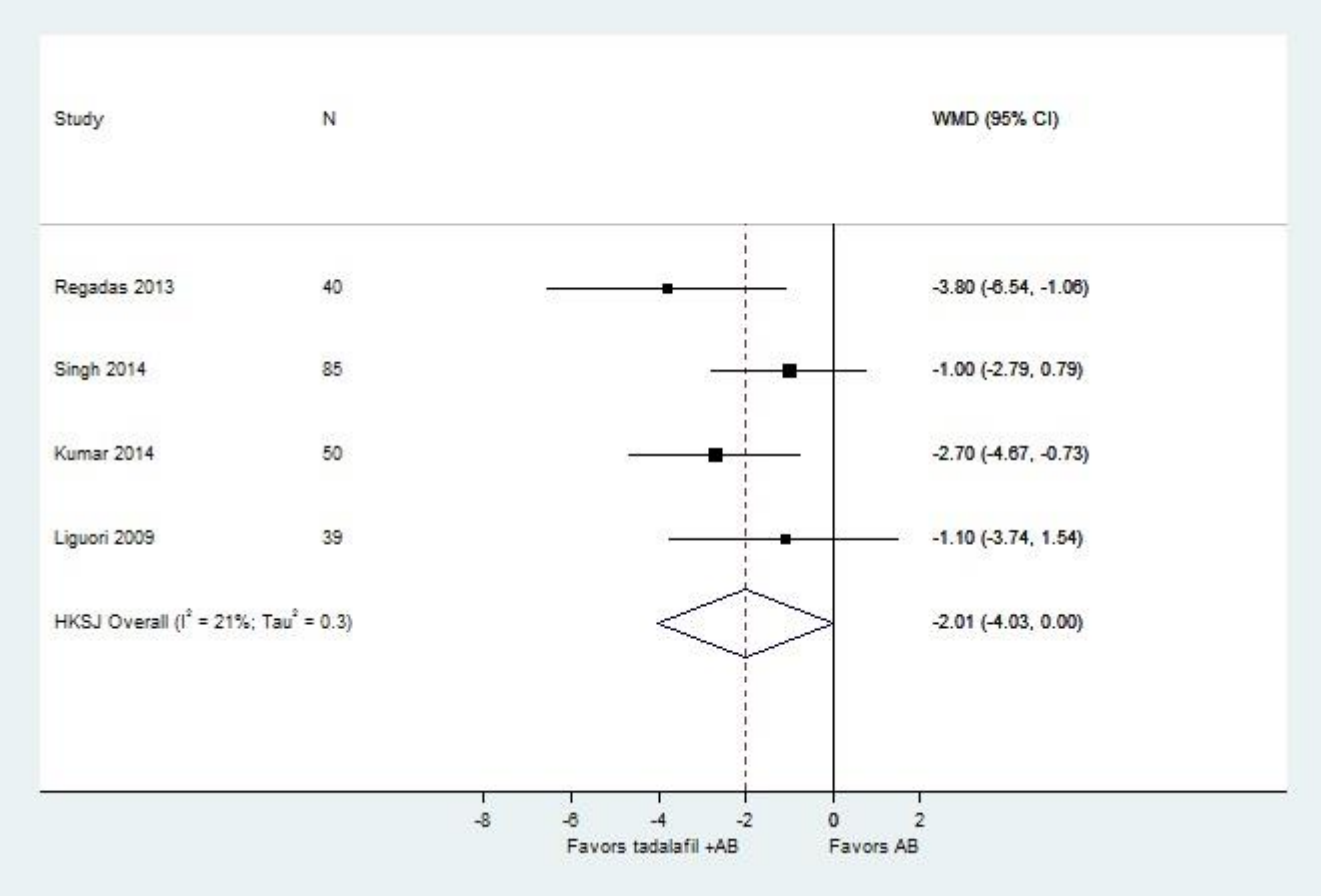
Adjunctive Efficacy of Tadalafil

Figure G2. I-PSS scores, mean change from baseline: combined tadalafil + alpha-blocker vs. alpha-blocker



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Comparative Effectiveness of Tadalafil Versus Tamsulosin

Figure G3. I-PSS scores, mean change from baseline: tadalafil vs. tamsulosin

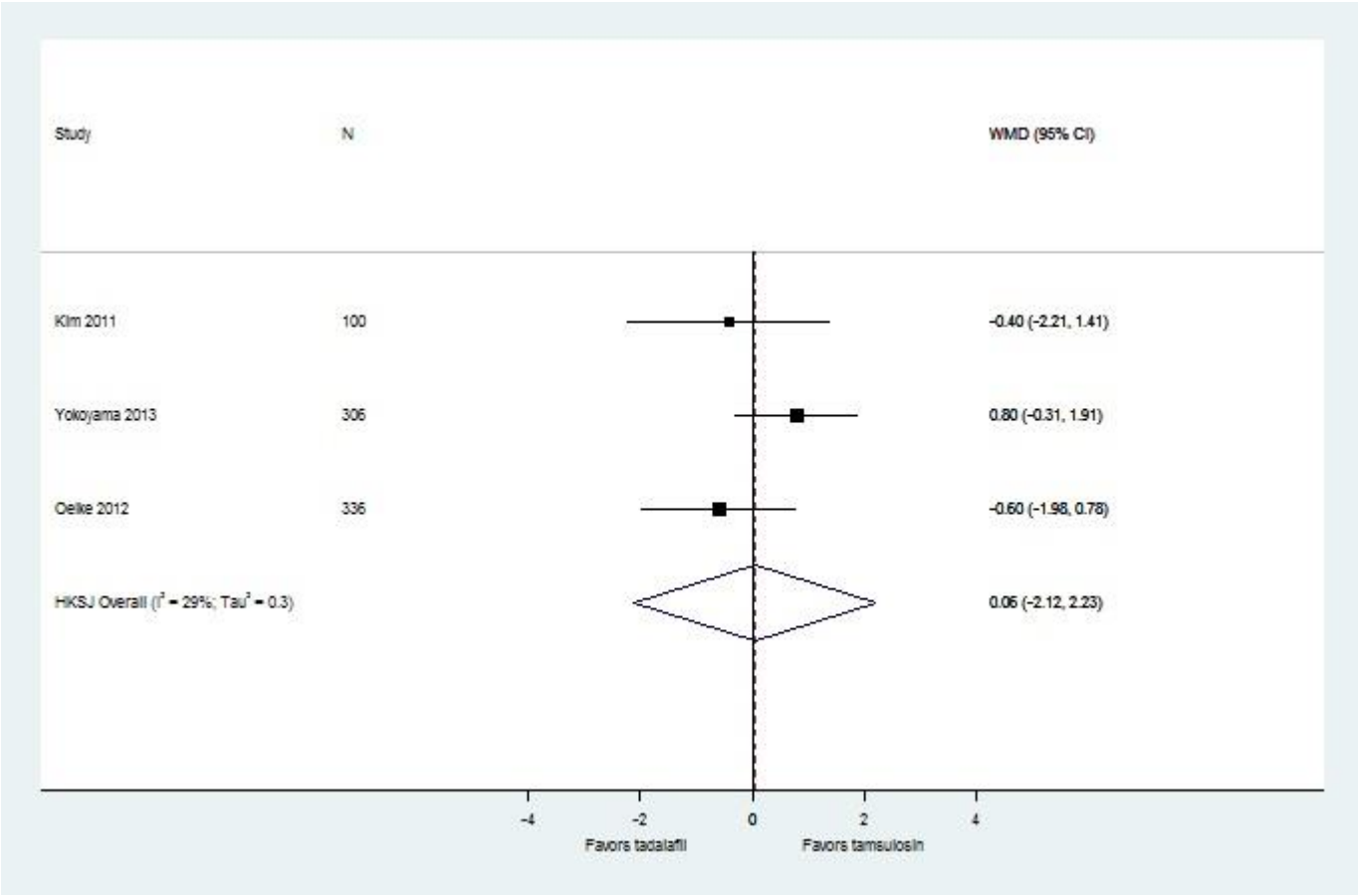

Table G5. Strength of evidence assessments: sildenafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Sildenafil 50-100 mg vs. placebo	I-PSS/AUA-SI, *mean change from baseline*	1 (341)	MD -4.40 (-6.87 to -1.93)	Low	Direct	Precise	Unknown	Undetected[a]	Strong strength of association	Low
	BII, *mean change from baseline*	1 (351)	MD -1.1 [CI NR, P <.0001)]	Low	Direct	Precision unclear	Unknown	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (351)	MD -0.7 [CI NR, P <.0001)]	Low	Direct	Precision unclear	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (369)	RR 0.80 (0.46 to 1.38)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (369)	RR 1.59 (0.59 to 4.28)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	1 (369)	RR 1.22 (0.99 to 1.51)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
Combined sildenafil 25-50 mg with any alpha-blocker vs. any alpha-blocker	I-PSS/AUA-SI, *mean change from baseline*	3 (233)	WMD -1.73 [-4.76 to 1.30]3 trials MD -1 [CI NR] 1 trial	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	2 (132)	Ozturk 2012 MD = -0.10 [-0.47, 0.27] Tuncel 2010 MD = -1.20 [-1.51, -0.89]	High	Direct	Imprecise	Inconsistent	Undetected[a]	NA	Insufficient
	Overall withdrawals	2 (141)	Ozturk 2012 RR = 1.67 [0.42, 6.60] Kaplan 2007 RR = 1.43 [0.27, 7.67]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	2 (141)	Ozturk 2012 RR not estimable Kaplan 2007 RR = 1.43 [0.27, 7.67]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
Sildenafil 25-50 mg vs. any alpha-blocker	I-PSS/AUA-SI, *mean change from baseline*	2 (181)	Abolyosr 2013 MD = 1.10 [-0.70, 2.90] Kaplan 2004 MD = 0.70 [-1.72, 3.12]	High	Direct	Imprecise	Consistent	Undetected[a]	NA	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (40)	MD = 0.80 (-1.18 to -0.42)	High	Direct	Precise	Unknown	Undetected[a]	NA	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
	Overall withdrawals	1 (45)	RR 0.95 (0.15 to 6.13)	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (45)	RR 0.95 (0.15 to 6.13)	High	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	NR							NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial. This trial has been included, so we detected no publication bias.

AUR=acute urinary retention; BII = BPH Impact Index; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Adjunctive Efficacy of Sildenafil

Figure G4. I-PSS scores, mean change from baseline: combined sildenafil + alpha-blocker vs. alpha-blocker

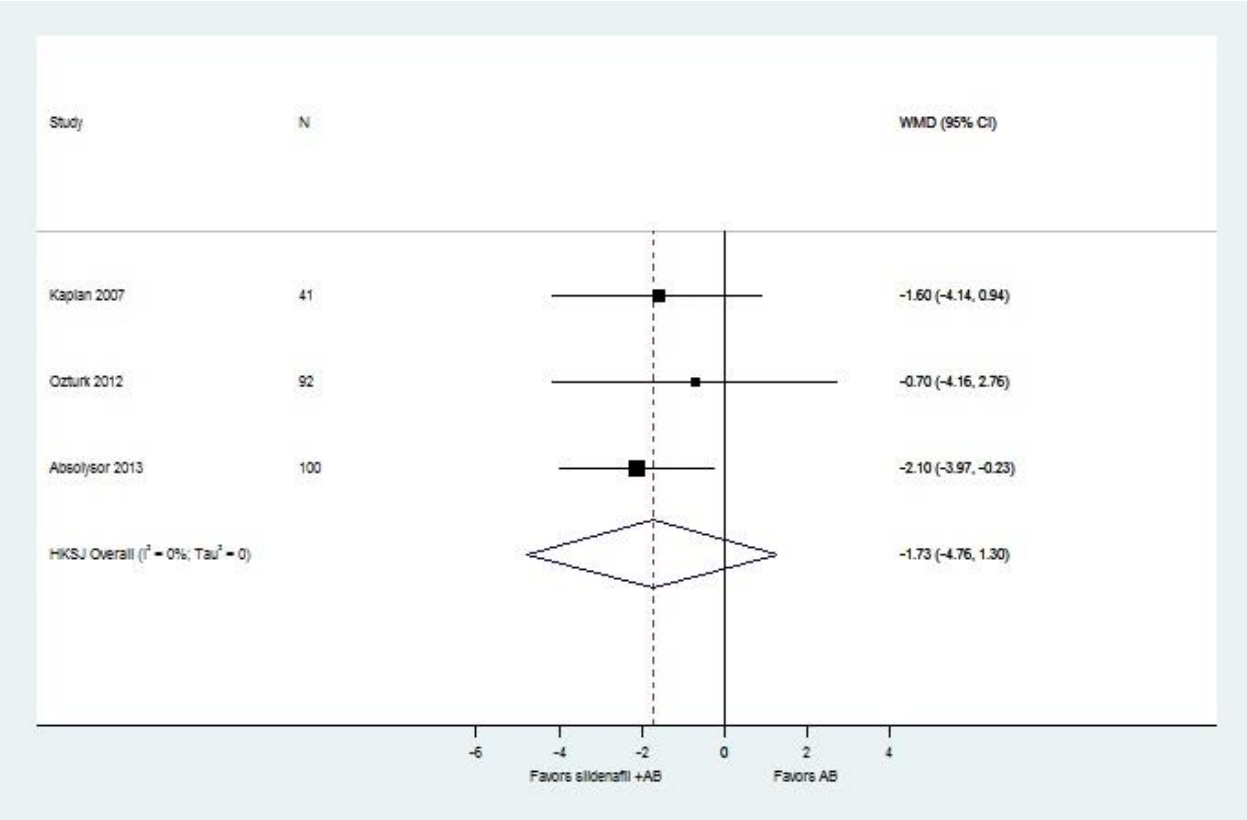

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Table G6. Strength of evidence assessments: vardenafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Optional Compo-nents	Evidence Rating
Vardenafil 20 mg vs. placebo	I-PSS/AUA-SI, *mean change from baseline*	1 (214)	MD -2.3 (-3.64 to -0.90)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Low
	Overall withdrawals	1 (222)	RR = 0.96 (0.47 to 1.95)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (222)	RR = 4.67 (1.03 to 21.11)	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
	Participants with ≥1 adverse effect	1 (222)	RR = 1.86 (1.11 to 3.11)	Low	Direct	Precise	Unknown	Undetected[a]	NA	Low
Combined vardenafil 10 mg with any alpha-blocker vs. any alpha-blocker	I-PSS/AUA-SI, *mean change from baseline*	1 (60)	MD = -2.10 (-4.76 to 0.56)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Overall withdrawals	1 (60)	RR = 0.32 (0.01 to 7.61)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Withdrawals due to adverse effects	1 (60)	RR = 0.32 (0.01 to 7.61)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient
	Participants with ≥1 adverse effect	1 (60)	RR = 1.50 (0.27 to 8.34)	Low	Direct	Imprecise	Unknown	Undetected[a]	NA	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial that has been included. We detected no publication bias.

AUR=acute urinary retention; BII = BPH Impact Index; I-PSS/AUA-SI= International Prostate Symptom Scale/American Urological Association Symptom Index; MD=mean difference; QoL=quality of life; RR=risk ratio; SMD=standardized mean difference; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

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Appendix H. References for Appendixes

1. Seki N, Takahashi R, Yamaguchi A, et al. Non-inferiority of silodosin 4mg once daily to twice daily for storage symptoms score evaluated by the International Prostate Symptom Score in Japanese patients with benign prostatic hyperplasia: A multicenter, randomized, parallel-group study. Int J Urol 2015 01 Mar;22(3):311-6. PMID: 2015682057.
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