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Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia (Review)

Pattanaik S, Mavuduru RS, Panda A, Mathew JL, Agarwal MM, Hwang EC, Lyon JA, Singh SK, Mandal AK

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Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia
(Review)

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[Intervention Review]

Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia

Smita Pattanaik¹, Ravimohan S Mavuduru², Arabind Panda³, Joseph L Mathew⁴, Mayank M Agarwal², Eu Chang Hwang⁵, Jennifer A Lyon⁶, Shrawan K Singh², Arup K Mandal²

¹Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. ²Department of Urology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. ³Department of Urology, Christian Medical College, Vellore, India. ⁴Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India. ⁵Department of Urology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. ⁶Library Services, Children's Mercy Hospital, Kansas City, Missouri, USA

Contact: Ravimohan S Mavuduru, Department of Urology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. ravismi2003@yahoo.com.

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH) refers to non-malignant enlargement of the prostate gland that may cause bothersome lower urinary tract symptoms (LUTS). Alpha-blockers (ABs) and 5-alpha reductase inhibitors (5-ARIs) are the mainstay of medical treatment. Recently, phosphodiesterase inhibitors (PDEIs) that so far have been used mainly to treat erectile dysfunction were introduced to treat male LUTS.

Objectives

To assess the effects of PDEIs compared to placebo and other standard of care drugs (ABs and 5-ARIs) in men with LUTS consistent with BPH.

Search methods

We conducted a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Web of Science, and clinical trials registries of the World Health Organization (WHO) and the National Institutes of Health (NIH) (updated 2 August 2018). We performed citation tracking and handsearching of abstracts and conference proceedings. We also contacted study authors to ask for additional information.

Selection criteria

We considered for inclusion in this systematic review randomised controlled trials (RCTs) comparing PDEIs versus placebo, ABs, or 5-ARIs for at least four weeks in men with BPH-LUTS.

Data collection and analysis

Three review authors independently screened the literature and extracted data. Primary outcomes were effects on urinary symptoms as assessed by the International Prostate Symptom Score (IPSS-total; score ranging from 0 to 35, with higher values reflecting more symptoms), urinary bother as assessed by the Benign Prostatic Hyperplasia Impact Index (BPHII; score ranging from 0 to 13, with higher values reflecting more bother), and adverse events (AEs). We used GRADE to rate the quality of evidence. We considered short-term (up to 12 weeks) and long-term (12 weeks or longer) results separately.

Main results

We included a total of 16 randomised trials in this review. The results for primary outcomes are as follows.

PDEI versus placebo: PDEIs may result in a small improvement in IPSS-total score (mean difference (MD) 1.89 lower, 95% confidence interval (CI) 2.27 lower to 1.50 lower; $n = 4293$; low-quality evidence) compared to placebo, and may reduce the BPHII score slightly (MD 0.52 lower, 95% CI 0.71 lower to 0.33 lower; $n = 3646$; low-quality evidence). Rates of AEs may be increased (risk ratio (RR) 1.42, 95% CI 1.21 to 1.67; $n = 4386$; low-quality evidence). This corresponds to 95 more AEs per 1000 participants (95% CI 47 more to 151 more per 1000). Study results were limited to a treatment duration of six to 12 weeks.

PDEI versus AB: PDEIs and ABs probably provide similar improvement in IPSS-total score (MD 0.22 higher, 95% CI 0.49 lower to 0.93 higher; $n = 933$; moderate-quality evidence) and may have a similar effect on BPHII score (MD 0.03 higher, 95% CI 1.10 lower to 1.16 higher; $n = 550$; low-quality evidence) and AEs (RR 1.35, 95% CI 0.80 to 2.30; $n = 936$; low-quality evidence). This corresponds to 71 more AEs per 1000 participants (95% CI 41 fewer to 264 more per 1000). Study results were limited to a treatment duration of six to 12 weeks.

PDEI and AB versus AB alone: the combination of PDEI and AB may provide a small improvement in IPSS-total score (MD 2.56 lower, 95% CI 3.92 lower to 1.19 lower; $n = 193$; low-quality evidence) compared to AB alone. We found no evidence for BPHII scores. AEs may be increased (RR 2.81, 95% CI 1.53 to 5.17; $n = 194$; moderate-quality evidence). This corresponds to 235 more AEs per 1000 participants (95% CI 69 more to 542 more per 1000). Study results were limited to treatment duration of four to 12 weeks.

PDEI and AB versus PDEI alone: the combination of PDEI and AB may provide a small improvement in IPSS-total (MD 2.4 lower, 95% CI 6.47 lower to 1.67 higher; $n = 40$; low-quality evidence) compared to PDEI alone. We found no data on BPHII or AEs. Study results were limited to a treatment duration of four weeks.

PDEI and 5-ARI versus 5-ARI alone: in the short term (up to 12 weeks), the combination of PDEI and 5-ARI probably results in a small improvement in IPSS-total score (MD 1.40 lower, 95% CI 2.24 lower to 0.56 lower; $n = 695$; moderate-quality evidence) compared to 5-ARI alone. We found no evidence on BPHII scores or AEs. In the long term (13 to 26 weeks), the combination of PDEI and 5-ARI likely results in a small reduction in IPSS-total score (MD 1.00 less, 95% CI 1.83 lower to 0.17 lower; $n = 695$; moderate-quality evidence). We found no evidence about effects on BPHII scores. There may be no difference in rates of AEs (RR 1.07, 95% CI 0.84 to 1.36; $n = 695$; low-quality evidence). This corresponds to 19 more AEs per 1000 participants (95% CI 43 fewer to 98 more per 1000).

We found no trials comparing other combinations of treatments or comparing different PDEI agents.

Authors' conclusions

Compared to placebo, PDEI likely leads to a small reduction in IPSS-total and BPHII scores, with a possible increase in AEs. There may be no differences between PDEI and AB with regards to improvement in IPSS-total, BPHII, and incidence of AEs. There appears to be no added benefit of PDEI combined with AB compared to PDEI or AB alone or PDEI combined with 5-ARI compared to ARI alone with regards to urinary symptoms. Most evidence was limited to short-term treatment up to 12 weeks and of moderate or low certainty.

PLAIN LANGUAGE SUMMARY

Phosphodiesterase inhibitors for treatment of urinary problems in men with benign prostatic hyperplasia

Review question

What are the effects of phosphodiesterase inhibitors compared to other medications, in men with urinary symptoms, that are thought to be due to an enlarged prostate?

Background

Problems related to urination, especially in older men, are often due to benign prostatic hyperplasia. Medications like alpha-blockers and 5-alpha reductase inhibitors are commonly used to treat these symptoms. They help to control symptoms but can have unwanted effects. Phosphodiesterase inhibitors are medications that have been used for a long time to help men have better erections. They may also help to improve urinary symptoms in men with benign prostatic hyperplasia.

Search date

We searched randomised trials, that studied these treatments, up to August 2, 2018.

Study characteristics

We found a total of 16 studies. They included mostly men, older than 60 years of age, with moderate, to severe urinary symptoms. Most studies were funded by the companies that make these drugs.

Key results

Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia (Review)

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Compared to placebo, phosphodiesterase inhibitors may make urinary symptoms a little better and reduce bother, but may also cause more unwanted drug effects.

There is probably no difference between phosphodiesterase inhibitors and alpha-blockers when it comes to improving urinary symptoms, and there may be no difference with regards to how bothersome symptoms are, or unwanted drug effects.

Taking a phosphodiesterase inhibitor with an alpha-blocker may improve urinary symptoms slightly more than taking alpha-blockers alone. We found no evidence regarding urinary bother. However, combination treatment probably causes a lot more unwanted drug effects.

Taking a phosphodiesterase inhibitor with an alpha-blocker may improve urinary symptoms slightly more than taking a phosphodiesterase inhibitor alone. We found no evidence regarding bother or unwanted drug effects.

In the short term (up to 12 weeks), the combination of a phosphodiesterase inhibitor with a 5-alpha reductase inhibitor probably makes urinary symptoms a little better compared to taking a 5-alpha reductase inhibitor alone, but the effect may be too small to notice. We found no evidence on bother, nor on rates of unwanted drug effects. When taken longer (13 to 26 weeks), combination treatment probably also improves urinary symptoms slightly to a degree that may not be noticeable. We found no evidence regarding urinary bother. Unwanted drug effects may be similar.

We found no evidence for other combination treatments or comparing different phosphodiesterase inhibitors. Most studies investigated only short-term use of these drugs (up to 12 weeks); therefore, long-term effects are largely unknown.

Quality of evidence

We mostly rated the quality of evidence as moderate or low, meaning that we are somewhat or quite unsure of the true results. The real effects may be similar or quite different.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. PDEI compared to placebo for lower urinary tract symptoms consistent with benign prostatic hyperplasia

PDEI compared to placebo for LUTS consistent with BPH for short-term use (up to 12 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI

Comparator: placebo

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with PDEI
IPSS-total score Assessed with International Prostate Symptom Score Scale from 0 (best: not at all) to 35 (worst: almost always) Follow up: range 6 to 12 weeks	4293 (11 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	-	Mean change in IPSS-total scores ranged from -5.1 to -1.2	MD 1.89 lower (2.27 lower to 1.5 lower)
BPHII score Assessed with BPHII questionnaire Scale from 0 (best: none) to 13 (worst: a lot or all the time) Follow-up: range 6 to 12 weeks	3646 (8 RCTs)	⊕⊕⊖⊖ LOW ^{a,c}	-	Mean change in BPHII scores ranged from -2 to -0.6	MD 0.52 lower (0.71 lower to 0.33 lower)
Adverse events Assessed with any event Follow-up: range 6 to 12 weeks	4386 (11 RCTs)	⊕⊕⊖⊖ LOW ^{a,b,d}	RR 1.42 (1.21 to 1.67)	Study population 226 per 1000	95 more per 1000 (47 more to 151 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MCID: minimum clinically important difference; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bDowngraded for possible publication bias based on funnel plot asymmetry.

^cClinically important imprecision; 95% CI crosses MCID of 0.5.

^dClinically important heterogeneity with I^2 of 50%.

Summary of findings 2. PDEI compared to alpha-blockers for LUTS associated with BPH

PDEI compared to alpha-blockers for LUTS consistent with BPH for short-term use (up to 12 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI

Comparator: alpha-blockers

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with alpha-blockers	Risk difference with PDEI
IPSS-total score Assessed with International Prostate Symptom Score Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: range 8 to 12 weeks	933 (4 RCTs)	⊕⊕⊕⊕ MODERATE ^a	-	Mean change in IPSS-total scores ranged from -5.7 to -5.35	MD 0.22 higher (0.49 lower to 0.93 higher)
BPHII score Assessed with BPHII questionnaire Scale from 0 (best: none) to 13 (worst: a lot or all the time) Follow-up: mean 12 weeks	550 (2 RCTs)	⊕⊕⊕⊕ LOW ^{a,b,c}	-	Mean change in BPHII score was -1.6	MD 0.03 higher (1.1 lower to 1.16 higher)

Adverse events Follow-up: range 8 to 12 weeks	786 (4 RCTs)	⊕⊕⊕⊕ LOW ^{a,b,c}	RR 1.35 (0.80 to 2.30)	Study population	
				203 per 1000	71 more per 1000 (41 fewer to 264 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bClinically important heterogeneity.

^cClinically important imprecision likely due to inconsistency.

Summary of findings 3. PDEI plus alpha-blocker compared to alpha-blockers alone for LUTS associated with BPH (short-term)

Combination of PDEI with alpha-blocker compared to alpha-blockers alone for LUTS consistent with BPH for short-term use (up to 12 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI + alpha-blockers

Comparator: alpha-blockers

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with alpha-blockers alone	Risk difference with PDEI plus alpha-blocker
IPSS-total score Assessed with International Prostate Symptom Score	193 (4 RCTs)	⊕⊕⊕⊕ LOW ^{a,b}	-	Mean change in IPSS-total scores ranged from -6.7 to -3.62	MD 2.56 lower (3.92 lower to 1.19 lower)

Scale from 0 (best: not at all) to 35 (worst: almost always)					
Follow-up: range 4 to 12 weeks					
BPHII score Assessed with BPHII questionnaire		-	-	-	-
Scale from 0 (best: none) to 13 (worst: a lot or all the time)					
Adverse effects Follow-up: range 4 to 12 weeks	194 (4 RCTs)	⊕⊕⊕⊕ MODERATE ^a	RR 2.81 (1.53 to 5.17)	Study population 130 per 1000	235 more per 1000 (69 more to 542 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MCID: maximum clinically important difference; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bClinically important imprecision; 95% CI crosses MCID of 3.0

Summary of findings 4. PDEI plus an alpha-blocker compared to PDEI alone for LUTS associated with BPH (short-term)

Combination of PDEI with an alpha-blocker compared to PDEI alone for LUTS consistent with BPH for short-term use (up to 12 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI + alpha-blockers

Comparator: PDEI

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with PDEI alone	Risk difference with PDEI plus an alpha-blocker
IPSS-total score Assessed with International Prostate Symptom Score Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 4 weeks	40 (1 RCT)	⊕⊕⊕⊕ LOW ^{a,b}	-	Mean change in IPSS-total score was -3.95	MD 2.4 lower (6.47 lower to 1.67 higher)
BPHII score Assessed with BPHII questionnaire Scale from 0 (best: none) to 13 (worst: a lot or all the time)		-	-	-	-
Adverse events		-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bDowngraded for clinically important imprecision; 95% CI crosses MCID of 3.

Summary of findings 5. PDEI + 5-ARI compared to 5-ARI alone for LUTS associated with BPH (short-term)

Combination of PDEI with 5-ARI compared to 5-ARI alone for LUTS consistent with BPH for short-term use (up to 12 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI + 5-ARI

Comparator: 5-ARI

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 5-ARI alone	Risk difference with PDEI + 5-ARI
IPSS-total score Assessed with International Prostate Symptom Score Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 12 weeks	695 (1 RCT)	⊕⊕⊕⊖ MODERATE ^{a,b}	-	Mean change in IPSS-total score was -3.8	MD 1.4 lower (2.24 lower to 0.56 lower)
BPHII score Assessed with BPHII questionnaire Scale from 0 (best: none) to 13 (worst: a lot or all the time)		-	-	-	-
Adverse events		-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

5-ARI: 5-alpha reductase inhibitor; BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bDowngraded for clinically important imprecision.

Summary of findings 6. PDEI + 5-ARI compared to 5-ARI alone for LUTS associated with BPH (long-term)

Combination of PDEI with 5-ARI compared to 5-ARI alone for LUTS consistent with BPH in long-term use (26 weeks)

Patient: men with LUTS consistent with BPH

Setting: outpatient

Intervention: PDEI + 5-ARI

Comparator: 5-ARI

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 5-ARI alone	Risk difference with PDEI + 5-ARI
IPSS-total score Assessed with International Prostate Symptom Score Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 26 weeks	695 (1 RCT)	⊕⊕⊕⊖ MODERATE ^{a,b}	-	Mean change in IPSS-total score was -4.5	MD 1 lower (1.83 lower to 0.17 lower)
BPHII score Assessed with BPHII questionnaire Scale from 0 (best: none) to 13 (worst: a lot or all the time)		-	-		
Adverse events Follow-up: mean 26 weeks	695 (1 RCT)	⊕⊕⊖⊖ LOW ^{a,b}	RR 1.07 (0.84 to 1.36)	Study population 271 per 1000	19 more per 1000 (43 fewer to 98 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

5-ARI: 5-alpha reductase inhibitor; BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MD: mean difference; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded for study limitations.

^bDowngraded for clinically important imprecision.

BACKGROUND

Description of the condition

Benign prostatic hyperplasia (BPH) commonly presents with lower urinary tract symptoms (LUTS) (Gerraway 1991). Erectile dysfunction (ED) is often associated with BPH-LUTS and negatively impacts the quality of life in aging males (Rosen 2003). Large-scale epidemiological studies conducted across various ethnic backgrounds have described a strong association between LUTS and ED (Braun 2000; Braun 2003; Li 2005; Martin-Morales 2001; Mondul 2008; Rosen 2003; Rosen 2009). The presence of risk factors like diabetes, hypertension, obesity, metabolic syndrome, cardiovascular illness, depression, and previous pelvic surgery increases the prevalence of both BPH-LUTS and ED in older men (Gerraway 1991). However, LUTS has been proposed as an independent risk factor for ED independent of ageing and other comorbidity-related risk factors (Braun 2000; MacFarlane 1996; McVary 2005a; Ponholzer 2004; Rosen 2003). It has also been proposed that ED is more frequent in individuals with severe LUTS, and that the severity of both conditions is often concordant (McVary 2005a; McVary 2005b; Mondul 2008). Several theories have been proposed to suggest a plausible biological link between LUTS and ED (Andersson 2011), although the association between BPH-LUTS and ED in elderly men does not necessarily establish a cause-and-effect relationship. The efficacy of phosphodiesterase inhibitors (PDEIs) in alleviating BPH-LUTS also supports the suggestion of a common pathophysiology affecting simultaneously, the vascular and autonomic systems of pelvic structures, like bladder, prostatic tissue, and urethra (Guliano 2012). BPH-LUTS-ED is increasingly considered a disease complex - a popular concept in the urology fraternity, with the potential for treatment with a single designer drug (Calogero 2018; Hatzimouratidis 2014).

In the last two decades, evidence emerging from preclinical studies suggests a unified pathophysiology and the presence of molecular targets in anatomical structures associated with both conditions (Fibbi 2010; Filippi 2007; Hedlund 2005; Kedia 2009; Kedia 2011a; Kedia 2011b; Truss 1996; Uckert 2007; Uckert 2009). Proposed common pathophysiological mechanisms for BPH-LUTS and ED include (1) insufficient nitric oxide (NO) availability, (2) overactivity of Rho-kinase, (3) autonomic dysregulation, (4) atherosclerotic pelvic vascular disease, (5) inflammation of lower urinary tract tissue, and (6) alteration in the androgenic environment. Reduced availability of NO could result from reduced endothelial nitric oxide synthase (eNOS) or neuronal nitric oxide synthase (nNOS) or its increased degradation due to the presence of reactive oxygen species (Barton 1997; Cai 2000). It has been reported that NOS expression and subsequent reduction in NO are reduced in the transition zone of the prostate in BPH, compared to the normal prostate (Bloch 1997). Reduced NO has been linked with prostatic smooth muscle hyperplasia, increasing smooth muscle contractile forces at the bladder neck and prostatic urethra, hypoxia of the pelvic organs, and autonomic dysregulation due to inadequate dilatation of the vasa vasorum and the vasa nervorum (Guliano 2012; Orabi 2011). Hypoxia upregulates the Rho-A/Rho-A calcium-sensitising kinase (ROCK) system, and it has been proposed to increase smooth muscle proliferation while inhibiting smooth muscle contractility (Ree 2003). Many of these converging mechanisms are believed to cause microvascular dysfunction altering normal endothelial and neural function and thereby affecting "global pelvic physiology". This has been put forth as the

common pathophysiological denominator for LUTS and ED (Celleck 2014). However, the relative contribution of each of these proposed mechanisms leading to microvascular dysfunction resulting in BPH-LUTS and/or ED is not known, although improvement in ED with treatment of LUTS has been observed, and vice versa (Fonari 2017).

Endothelial dysfunction affecting the NO/cyclic guanosine monophosphate (cGMP) system has proved to play a central role in the pathophysiology of ED. The dramatic results of treatment with phosphodiesterase inhibitors have confirmed the proof of concept (McVary K 2006). The NO/cGMP pathway operating in the detrusor, bladder neck, prostatic tissue, prostatic urethra, penile tissue, penile urethra, and lower urinary tract vasculature has been the proposed target of PDEI in the context of BPH-LUTS-ED (Fibbi 2010; Filippi 2007; Hedlund 2005; Kedia 2009; Kedia 2011a; Kedia 2011b; Truss 1996; Uckert 2007; Uckert 2009).

Description of the intervention

The current standard of pharmacological management for BPH-LUTS includes alpha-1 blockers (generically referred to as alpha-blockers (ABs) in this review) with or without 5-alpha reductase inhibitors (5-ARIs) (AUA 2010; EAU 2016). Anticholinergic drugs are sometimes prescribed to provide additional relief for overactive bladder (OAB)-like symptoms.

Alpha-blockers (ABs)

An important target for treatment of BPH-LUTS involves alpha-1 receptors (1A, 1B, and 1D) present in the smooth muscles at the bladder neck and the prostatic tissue. These act as internal sphincter. Alpha-1 blockers lower the sympathetic tone on smooth muscles at the bladder neck and the prostatic fibromuscular stroma, thereby attenuating the dynamic component of the obstruction and improving urinary outflow (Milani 2005). They improve the total International Prostate Symptom Score (IPSS-total) by 30% to 40% compared to 10% to 20% with placebo (Djavan 2004), and they increase the maximum urinary flow rate (Qmax) by 20% to 25%. Improvement in IPSS-total is about 50%, and improvement in Qmax is up to 40% in open-label studies (EAU 2013). Available drugs include alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin. These agents are considered equally efficacious, and the older agents should preferably be prescribed because of cost-effectiveness considerations (AUA 2010; EAU 2013). Adverse events (AEs) experienced with the use of ABs are mediated by both central and peripheral mechanisms, which include dizziness, headache, asthenia, postural hypotension, syncope, peripheral oedema, and retrograde ejaculation (Djavan 1999). Rates of discontinuation due to side effects range from 4% to 10% (Djavan 1999). Although these drugs have shown satisfactory improvement in LUTS and urinary flow, they have led to no improvement in ED. The efficacy of these drugs is reported to be maintained for about four years (McConnell 2003; Roehrborn 2006).

5-Alpha reductase inhibitors (5-ARIs)

These drugs inhibit the conversion of testosterone to 5-hydroxy testosterone. 5-ARIs are used in patients with an enlarged prostate, along with ABs to attenuate androgen-induced prostatic growth. They exert their effects by decreasing the mass of the prostate by 18% to 20%, thereby acting on the static component of the obstruction (Djavan 2011; Shibata 2017). They have also been shown to reduce serum prostate-specific antigen (PSA) levels by

50% over six months to one year of treatment (EAU 2013). These agents offer 15% to 30% improvement in maximum urinary flow rate compared to 10% to 15% with placebo (Roerborn 2002). They have a variable tolerability profile. The main side effects include ED, decreased libido, ejaculatory problems, and gynaecomastia (Andriole 2003), which is explained by the pharmacological action of the drug.

Both ABs and 5-ARIs alone, or in combination, are somewhat satisfactory in alleviating LUTS symptoms, but they do not improve and may lead to worsening of co-existing male sexual dysfunction (Brookes 2002). It has also been reported that men treated with combination treatment have continued medical treatment for BPH longer than those given single-drug treatment (Rensing 2017).

Phosphodiesterase inhibitors (PDEIs)

Phosphodiesterases (PDEs) comprise a group of 11 enzymes (PDE₁₋₁₁) expressed in a variety of tissues. They increase the intracellular level of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) by decreasing their degradation. PDE₅ is the prevalent enzyme in the penile vasculature and in other pelvic tissues. PDE₅ inhibitors do not have any direct vasorelaxant properties, but they increase NO released at neuronal-smooth muscle junctions (Bischoff 2004). The US Food and Drug Administration (FDA) has approved four PDEI agents - sildenafil (Viagra 1988), tadalafil (Cialis 2003), vardenafil (Levitra 2003; Staxyn 2010), and avanafil (Stendra 2012) - for treatment of ED, but has approved only two agents for use in pulmonary arterial hypertension - sildenafil - as described in Revatio 1998 - and tadalafil - as reported in Adicirca 2009. Approved doses of drugs to be used for ED on an "as and when required" basis are sildenafil 25, 50, or 100 mg; tadalafil 10 or 20 mg; vardenafil 10 or 20 mg; and avanafil 25, 50, or 100 mg before sexual intercourse. These drugs appear to have equivalent efficacy in the treatment of ED; therefore, the class effect is well established (Corona 2011). They differ in their profile of PDE isoenzyme inhibition (and hence their side effect profile) and in their duration of action (Lue 2007). Tadalafil is superior to others due to its longer duration of action ($t_{1/2}$ = 17.5 hours; total duration of action = 36 hours), and it causes fewer visual (700 times higher selectivity to inhibit PDE₅ than PDE₆ present in retina) and musculoskeletal side effects (minimal inhibition of PDE₁₁) (Meherotra 2007; Rezvanfar 2014). Tadalafil has been approved by the FDA (in October 2011) for treatment of BPH-LUTS with or without ED, at a dose of 2.5 or 5 mg daily (FDA 2011).

How the intervention might work

Truss 1996 first reported the presence of PDE₅ in the detrusor muscle using chromatographic methods. Immunolabelling and immunohistochemical studies have shown that PDE is expressed in the detrusor muscle, in pelvic vessels supplying these smooth muscles, in vascular smooth muscle of the prostatic tissue, and in the prostatic urethra (Ho 1998; Uckert 2006; Uckert 2011). Human prostatic glandular and subglandular areas have been shown to express both PDE₅ and PDE₁₁ (Fibbi 2010). Gacci 2011 and Oger 2010 found that expression of PDE₅-RNA was much less in prostatic tissue than in detrusor and penile tissue. cGMP and nitric oxide are important inhibitory neurotransmitters in the smooth muscle of the urethra, and strong PDE₅ immunoreactivity has been demonstrated in the smooth muscle cells of the prostatic and non-prostatic urethra (Fibbi 2010; Kedia 2008). For bladder detrusor function, cAMP seems more important than cGMP, but

PDE₅ immunoreactivity has been noted in endothelial and smooth muscle cells of the vasculature and in smooth muscle cells of the muscle bundles (Filippi 2007). Isolated tissue experiments have shown the relaxant effect of PDE₅ on the bladder neck (Bittencourt 2009; Guiliano 2013b; Werkstrom 2009). The presence of PDE₅ has been demonstrated in the lower urinary tract vasculature, localised to smooth muscle cells of larger arteries, endothelial cells lining the arterial lumen, and the endothelium of smaller arteries (Fibbi 2010). PDEs are found to be present at various sites in the lower urinary tract, namely, the urinary bladder (bladder dome comprising the detrusor - bladder neck smooth muscles forming the internal sphincter); the prostate (prostatic smooth muscles in the transitional zone surrounding the prostatic urethra - prostatic glandular epithelial cells and stromal tissue); the urethra (urethral smooth muscles); and blood vessels and nerve endings supplying these structures (Gacci 2011). Expressions of PDE in the lower urinary tract seem to be ubiquitous, although the density of these enzymes may vary from place to place. The extensive presence of PDE enzymes, especially PDE₅, in lower urinary tract tissue, and their effects on various smooth muscles are favourable findings suggesting a new drug target for treatment of LUTS consistent with BPH. However, it is not clear if their preponderance suggests their dominance in controlling LUT physiology and subsequent pathophysiology.

Sairam 2002 presented the first evidence for the proof of concept in humans in an observational study. Since then, evidence in favour of PDE₅ inhibition in BPH-LUTS has been accumulating from preclinical and clinical studies. Clinical studies have been conducted in populations of varied ethnic origin and have demonstrated a beneficial effect of PDEI in BPH-LUTS with variable success.

Why it is important to do this review

- The current standard of medical treatment for LUTS consistent with BPH (AB with or without 5-ARI) is somewhat satisfactory as far as efficacy is concerned, but is poorly tolerated because of vascular side effects (Laborde 2009). The efficacy of these drugs tends to decrease over time (McConnell 2003; Roerborn 2006). Moreover, they adversely affect male sexual function, causing decreased libido (3% to 6% with 5-ARI), ED (6% to 8% with 5-ARI), decreased ejaculatory volume (1% to 4% with 5-ARI), and retrograde ejaculation (8% to 28% with AB) (Laborde 2009).
- PDEIs have shown their efficacy in relieving LUTS symptoms in various types of clinical studies including observational studies, uncontrolled clinical trials, randomised open-label trials, and randomised placebo-controlled trials.
- PDEIs, ABs, and 5-ARIs act through different components in the pathophysiology of LUTS consistent with BPH. The PDE₅ inhibitor, tadalafil, is a relatively new addition, and a thorough examination of its efficacy is needed to assist clinicians in choosing the best drug and drug combination for treatment.
- Long-term effects of PDEIs in maintaining their efficacy in LUTS, effects on disease progression, and adverse outcomes of their use are not clear.

Therefore, a systematic review of emerging evidence is needed to allow an overall assessment of the efficacy and safety of these agents.

OBJECTIVES

To assess the effects of PDEIs compared to placebo and other standard of care drugs (ABs and 5-ARIs) in men with LUTS consistent with BPH.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion in the review, randomised controlled clinical trials (RCTs) in which participants and study investigators and/or outcome assessors were masked to the interventions. Studies that evaluated one (or more) of the below mentioned outcome measures were deemed eligible for analysis. We included eligible studies regardless of their publication status or language of publication.

Types of participants

We looked for studies including men with BPH and complaints of significant LUTS as evaluated by an International Prostate Symptom Score-total (IPSS-total) of 12 or more (from the American Urologic Association (AUA)) with or without concomitant ED.

Types of interventions

Studies conducted the following comparisons.

- PDEI versus placebo (used for at least 4 weeks).
- PDEI versus other standard medical treatment for BPH-LUTS (AB and 5-ARI).
- PDEI in combination with other standard medical treatment for BPH-LUTS versus either treatment alone.

Specific comparison groups were as follows.

- PDEI versus placebo.
- PDEI versus AB.
- PDEI versus 5-ARI.
- PDEI + AB versus PDEI alone.
- PDEI + AB versus AB alone.
- PDEI + 5-ARI versus PDEI alone.
- PDEI + 5-ARI versus 5-ARI alone.
- PDEI + AB + 5-ARI versus AB + 5-ARI.
- Comparison of different PDEI agents for treatment of BPH-LUTS.

Types of outcome measures

Primary outcomes

- Total International Prostate Symptom (IPSS-total) score
- Benign Prostatic Hyperplasia Impact Index (BPHII) score
- Adverse events (AEs)

Secondary outcomes

- IPSS-quality of life score (IPSS-QOL)
- Acute urinary retention (AUR)

- Surgical interventions
- Other treatment-related harms

All outcomes were assessed for short-term (up to 12 weeks) and long-term (12 weeks and longer) use. We reported minimal clinically important differences (MCIDs) to show clinical relevance. For IPSS-total, we used an MCID of 3 (AUA 2010; Barry 1995); for BPHII, we used an MCID of 0.5 (Barry 1995).

Search methods for identification of studies

Electronic searches

We first searched electronic databases in October 2014; we periodically updated the search during conduct of the review, conducting the final update in August 2018. Our search included the Cochrane Central Register of Controlled Trials (CENTRAL; updated 2018 August 2) in the Wiley Cochrane Library; MEDLINE (Ovid®) (updated 2 August 2018); Embase (Elsevier) (updated 2 August 2018); and Science Citation Index Expanded via Web of Science™ (updated 2 August 2018). We also searched the clinical trials registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (updated 13 August 2018). We have detailed the search strategies used in Appendices 1 to 5 (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5).

Searching other resources

We inspected the references lists of all included RCTs and selected relevant reviews to look for more trials. We asked the authors of eligible RCTs for additional data from their study if these data were not reported in the published manuscripts. We asked investigators of unpublished trials for additional information. We handsearched relevant peer-reviewed journals (*Journal of Urology*, *BJU International*, *European Urology*, *Journal of Sexual Medicine*, *Urology Gold*; from January 2010 to August 2, 2018) and abstract books including contributions presented at congresses of international societies (e.g. American Urological Association, International Continence Society; from January 2010 to August 2, 2018) for additional information.

Data collection and analysis

Selection of studies

Four review authors (SP, RM, AP, and MMA) independently assessed relevant titles and abstracts, identified by the literature search, against predefined inclusion criteria. The same four review authors investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies or excluded studies. We resolved conflicts by discussion and by consensus.

We reviewed all English and non-English papers. We corresponded with original study authors to request any relevant additional information needed to determine the eligibility of a study for inclusion. When we identified that more than one publication of a trial existed, we grouped reports together and used the most complete data set. We sought help from the Cochrane Urology Group in resolving issues when needed. We have outlined the results of our search in Figure 1.

Figure 1. Study flow diagram.

Data extraction and management

Three review authors (SP, RM, and AP) independently abstracted data using a standardised data abstraction form that had been pilot-tested. Extracted data included study design; time period when the study was conducted; study setting; participant inclusion and exclusion criteria; participant age; sample size for each intervention group; details of interventions; details of outcomes relevant to the review; how outcomes were measured; time points at which they were measured; details of funding sources; declarations of interest among primary study authors; any published protocols; and any other study details relevant to risk of bias assessment. Data analysis was based on available trial data relevant to comparisons and outcomes of interest. We contacted authors of the primary studies for clarification of data and/or additional information if relevant data were missing from the published manuscripts. We finalised data analysis after discussion among the review authors (JLM, MMA, SKS, and AKM), and we resolved disagreements by consensus and in consultation with the Cochrane Urology Group.

Assessment of risk of bias in included studies

Two independent review authors (SP and JLM) assessed the quality and risk of bias (ROB) of included studies, without blinding to authorship or journal. We assessed the following items using the Cochrane method for assessing risk of bias ([Higgins 2011](#)), along with the 'Risk of bias' tool provided in RevMan 5.3.5 ([Revman 2014](#)).

- Random sequence generation (selection bias).
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting.
- Other sources of bias.

We judged risk of bias domains as low risk, high risk, or unclear risk, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We assessed risk of bias for each outcome within and across studies. We noted that the risk of bias for random sequence generation and allocation concealment was consistent across outcomes. However, we assessed risk of bias for blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting on an outcome-specific basis, as the risk of bias of each of these domains is likely to vary by outcome.

Based on the nature of the outcomes, we grouped them into (1) IPSS-total, BPHII, and IPSS-QOL; (2) AEs and other treatment-related harms; and (3) AUR and need for surgical intervention for assessment of risk of bias.

We have generated 'Risk of bias tables' for each included study and have presented a 'Risk of bias summary' in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): IPSS-total, BPHII, IPSS-QOL	Blinding of participants and personnel (performance bias): AE and treatment related harms	Blinding of participants and personnel (performance bias): Acute urinary retention and need for surgical intervention	Blinding of outcome assessment (detection bias): IPSS-total, BPHII, IPSS-QOL	Blinding of outcome assessment (detection bias): AE and treatment related harms	Blinding of outcome assessment (detection bias): Acute urinary retention and need for surgical intervention	Incomplete outcome data (attrition bias): IPSS-total, BPHII, IPSS-QOL	Incomplete outcome data (attrition bias): AE and treatment related harms	Incomplete outcome data (attrition bias): Acute urinary retention and need for surgical intervention	Selective reporting (reporting bias): IPSS-total, BPHII, IPSS-QOL	Selective reporting (reporting bias): AE and treatment related harms	Selective reporting (reporting bias): Acute urinary retention and need for surgical intervention	other bias
Bechara 2008	?	?	+	+	+	+	+	+	+	+	+	+	+	+	?
Brock 2013a	?	?	?	?	+	?	?	+	+	+	+	+	+	+	?
Casabe 2014	?	+	?	?	+	?	?	+	?	?	?	+	+	+	?
Dmochowski 2010	?	?	?	?	+	?	?	+	?	?	+	?	+	+	+
Egerdie 2012	+	+	+	+	+	+	+	+	?	?	?	+	+	+	?
Gacci 2012	+	?	+	+	+	+	+	+	+	+	+	?	+	+	?
Kim 2011	?	?	?	?	+	?	?	+	+	+	+	+	+	+	?
McVary 2007a	+	?	?	?	+	?	?	+	?	?	?	+	+	+	?
McVary 2007b	?	?	?	?	+	?	?	+	+	+	+	+	+	+	?
Olke 2012	?	?	+	+	+	+	+	+	?	?	?	+	+	+	?

Figure 2. (Continued)

May 2008	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oelke 2012	?	?	+	+	+	+	+	+	?	?	?	+	+	+	?
Porst 2011	?	?	+	+	+	?	?	+	+	+	+	+	+	+	+
Regadas 2013	?	?	?	?	+	?	?	+	+	+	+	?	+	+	+
Roehrborn 2008	?	?	+	+	+	?	?	+	?	?	?	+	+	+	?
Stief 2008	+	+	+	+	+	?	?	+	?	?	?	+	+	+	+
Takeda 2012	+	+	+	+	+	+	+	+	+	+	+	+	+	+	?
Tuncel 2010	?	?	?	?	+	?	?	+	+	+	+	+	+	+	+
Yokoyama 2013	?	?	?	?	+	?	?	+	?	?	?	+	+	+	?

Measures of treatment effect

We used Review Manager 5.3 to analyse data (Revman 2014). We combined data from RCTs for meta-analyses. We calculated the mean difference (MD) with 95% confidence interval (95% CI) for continuous outcomes and the risk ratio (RR) with 95% CI for dichotomous outcomes.

Unit of analysis issues

We considered parallel-design randomised controlled clinical trials as well as cross-over studies for inclusion in the review. We performed data extraction and analysis and risk of bias assessments for cross-over trials as per Section 16.4, in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The individual participant is considered a unit in this type of analysis, hence the unit of analysis issue is not relevant for this review.

Dealing with missing data

We contacted the authors of papers with missing data (studies, outcomes, summary data, individuals, measures of variance, or study level characteristics) to request missing or unreported data. We performed analysis using the intention-to-treat (ITT) principle. When we could not obtain data from the authors of incompletely reported papers, we excluded them from the review, citing the specific reason for the same. However, if pooled data were available for such studies, we included them in the analysis as published literature.

Assessment of heterogeneity

We regarded an I^2 value $> 50\%$ as showing considerable heterogeneity, and we dealt with this by using the random-effects model. Alternatively if we judged that clinical or study design heterogeneity was present, we conducted subgroup analyses to assess the robustness of pooled outcomes and conclusions.

Assessment of reporting biases

We attempted to obtain the protocols of included studies to assess selective outcome reporting. We constructed funnel plots (trial effect vs trial size) for comparisons including at least 10 studies to investigate the possibility of publication bias. We also looked at other relevant sources of bias.

Data synthesis

We used a fixed-effect model for analysis unless we noted statistically significant heterogeneity ($I^2 > 50\%$) between studies. We employed a random-effects model if heterogeneity existed. We used the inverse variance method for meta-analysis of continuous outcomes and the Cochran-Mantel-Haenszel method for meta-analysis of dichotomous outcomes. When a meta-analysis was not possible or was not appropriate, we prepared a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses.

- Participants with or without ED.
- Different PDEIs, namely, tadalafil versus vardenafil versus sildenafil.
- Different doses of PDEIs.

Sensitivity analysis

- We excluded RCTs without a run-in period

Among the included RCTs, some had incorporated a two- to four-week run-in period before providing the randomised study intervention. The placebo and/or active drug run-in period represents a potential source of bias because this may lead to selection of participants who are more compliant and/or less likely to experience AE. Therefore, we conducted a sensitivity analysis to explore the effect of the pre-intervention run-in period on effect size for various outcomes.

'Summary of findings' table

We rated the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, which takes into account criteria related not only to internal validity: study limitations (risk of bias), inconsistency, imprecision, and publication bias; but also to external validity: indirectness of results (Guyatt 2008). For each comparison, two review authors (SP and RM) independently rated the quality of evidence for each outcome as high, moderate, low, or very low, using GRADEproGDT software. SP, RM, and JLM constructed 'Summary of findings' tables and resolved discrepancies by consensus or, if needed, via arbitration by other

review authors (AP, SKS, and AKM). For each comparison, we have presented a summary of evidence for the main outcomes in a 'Summary of findings' table. This provides key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011; Schünemann 2013).

RESULTS

Description of studies

We have outlined search results in Figure 1. As per the protocol, we used nine comparison groups to evaluate the efficacy and safety of PDEI compared to placebo or existing treatments (alone or in combination). We segregated the included studies as per the comparison groups. Of the nine comparison groups, we could identify no studies for four groups.

- PDEI versus 5-ARI (group 3).
- PDEI + 5-ARI versus PDEI alone (group 6).
- PDEI + AB + 5-ARI versus AB + 5-ARI (group 8).
- Comparison of different PDEIs for treatment of BPH-LUTS (group 9).

We have presented detailed descriptions of the interventions in Table 1, and we have described baseline characteristics of the included studies in Table 2.

PDEI versus placebo

Through our search strategy, we identified 11 RCTs meeting the inclusion criteria (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007a; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Stief 2008; Takeda 2012; Tamimi 2010; Yokoyama 2013). We did not include one RCT, as we could not obtain data from study authors or could not impute data from available published literature (Tamimi 2010). We included in the analysis a total of 11 RCTs with 4293 participants (1576 in the placebo group, and 2717 in the PDEI treatment group). All RCTs were multi-centric clinical trials. They included elderly men with LUTS consistent with BPH living in various parts of North America, Europe, South America, Japan, and Korea. Five of the 11 RCTs were multi-national (Kim 2011; McVary 2007a; McVary 2007b; Stief 2008; Takeda 2012; Yokoyama 2013). Among the other studies, one was conducted in the USA (McVary 2007a; McVary 2007b), two in Japan (Takeda 2012; Yokoyama 2013), one in Korea (Kim 2011), and one in Germany (Stief 2008).

All included RCTs reported the racial origin of participants. About 85% to 87% of participants belonged to the white race, and 4% to 6% belonged to the black race, as reported in seven RCTs (Dmochowski 2010; Egerdie 2012; McVary 2007a; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Stief 2008). The remaining participants (7% to 11%) were Asian men included in three RCTs (Kim 2011; Takeda 2012; Yokoyama 2013).

RCTs included men older than 45 years with symptoms of BPH-LUTS, irrespective of their ED status. The mean age of participants in PDEI and placebo groups was 69.1 ± 8.4 and 62.02 ± 8.8 years, respectively. Two RCTs included participants with both BPH-LUTS

and ED (Egerdie 2012; McVary 2007a). Included participants had moderate to severe LUTS at the qualifying visit. Mean IPSS-total score in PDEI and placebo groups was 17.6 ± 5.5 and 17.5 ± 5.6 , respectively. Baseline characteristics included baseline LUTS severity, ED severity, prior AB or 5-ARI use, uroflow parameters, post-void residue (PVR), PSA, and demographic features. Six of the 11 RCTs reported participant characteristics including LUTS severity, proportions of participants with ED, severity of ED, and prior AB use status. Six RCTs did not report any of these participant characteristics (Dmochowski 2010; McVary 2007a; Roehrborn 2008; Stief 2008; Takeda 2012; Yokoyama 2013). The mean duration of BPH-LUTS and/or ED also was not described in many of the RCTs (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Roehrborn 2008; Stief 2008; Takeda 2012; Yokoyama 2013). Men with a history of BPH-LUTS longer than six months were considered for inclusion. RCTs had excluded participants with $Q_{max} < 4$ mL/s and > 15 mL/s, PSA > 10 ng/mL or positive prostatic biopsy with PSA between 4 and 10 ng/mL, use of 5-ARIs within the last three to six months, and other pelvic diseases or history of pelvic surgery within the preceding six months.

Nine of the 11 RCTs used the long-acting PDEI, tadalafil, whereas McVary 2007a used sildenafil and Stief 2008 used vardenafil. We were able to find one study that examined use of gisadenafil but were unable to retrieve data required for the meta-analysis (Tamimi 2010). We identified no studies for avanafil or udenafil. The dose of tadalafil studied ranged from 2.5 to 20 mg once daily, for sildenafil 50 to 100 mg once daily, and vardenafil 10 mg twice daily. The dose of tadalafil used most commonly was 5 mg per day (i.e. the FDA-approved highest dose for BPH-LUTS) (Cialis 2011). Four RCTs included an additional arm given 2.5 mg per day (Egerdie 2012; Roehrborn 2008; Takeda 2012; Yokoyama 2013). Dmochowski 2010 studied only one dose of tadalafil - 20 mg per day - and the primary outcome was the urodynamic parameter. Roehrborn 2008, a dose-ranging study, compared all dosages, namely, 2.5, 5, 10, or 20 mg per day, against placebo. McVary 2007a used sildenafil in a dose titration design but did not report the number of participants using 50 or 100 mg of the drug.

Most RCTs were short-term efficacy studies. The maximum study duration was 12 weeks (in 10/11 RCTs) and the minimum duration was eight weeks (Stief 2008). Two studies had an open-label extension (OLE) phase of up to 42 weeks - in Takeda 2012 - and 64 weeks in Roehrborn 2008. These studies used tadalafil at a dose of 5 mg per day in the OLE. Seven of 11 RCTs included a treatment-free washout period of four weeks for participants who were already receiving treatment at screening (Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Yokoyama 2013), but Takeda 2012 reported a washout period of two weeks. After the washout, investigators subjected these participants to a four-week single-blind placebo run-in period. However, the treatment-naïve participants were not subjected to any wash-out but only a four-week single-blind placebo run-in period. Three of 11 RCTs did not follow this pattern for enrolment. Two of them used only a drug-free washout period (Dmochowski 2010; Stief 2008), but they did not include a placebo run-in period. McVary 2007a neither included a washout period nor a run-in period. This study also did not specify whether participants were naïve or experienced to treatment.

The primary outcome in most RCTs was effect of PDEIs on LUTS, but for Dmochowski 2010, the primary outcome was change in the

urodynamic parameter for bladder outlet obstruction (BOO), and change in erectile function was the secondary outcome.

Pharmaceutical manufacturers of the active drugs (PDEIs) sponsored eight of 11 included RCTs comparing PDEIs versus placebo (Egerdie 2012; McVary 2007a; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Stief 2008; Takeda 2012; Yokoyama 2013), and manufacturers of the investigational drug presumably sponsored the remaining two RCTs, although published reports included no statement on trial sponsorship (Dmochowski 2010; Kim 2011). Apart from providing the logistics, study sponsors made significant contributions to design and conduct of the study, data acquisition, data analysis, interpretation of results, and preparation and final approval of the manuscript.

PDEI versus AB

We included four RCTs comprising 933 participants for this comparison (Kim 2011; Oelke 2012; Tuncel 2010; Yokoyama 2013). Three of these RCTs were included in the previous comparison and had three arms, namely, PDEI, AB, and placebo (Kim 2011; Oelke 2012; Yokoyama 2013). The only remaining RCT compared PDEI, AB, and a combination of the two (Tuncel 2010). Three RCTs used tadalafil 5 mg as the PDEI (Kim 2011; Oelke 2012; Yokoyama 2013), and one used sildenafil 25 mg (Tuncel 2010). Yokoyama 2013 included an additional tadalafil 2.5 mg arm. All researchers used PDEI as once-daily therapy, but the sildenafil study - Tuncel 2010 - used it four times weekly. The AB in all included studies was tamsulosin, although the dose was not uniform across studies. Two RCTs used 0.2 mg once daily (Kim 2011; Yokoyama 2013), whereas the other two used 0.4 mg once daily (Oelke 2012; Tuncel 2010). All participants included in Tuncel 2010 were treatment naïve; the other studies did not specify so and included a mixed cohort of previously treated and untreated participants. The tadalafil studies incorporated a drug washout period, followed by a placebo run-in period (Kim 2011; Oelke 2012; Yokoyama 2013). All studies examined short-term treatment provided over eight to 12 weeks.

PDEI versus 5-ARI

We found no studies that met the inclusion criteria for this comparison.

PDEI + AB versus AB alone

For this comparison, we included four RCTs involving a total of 193 participants (Bechara 2008; Gacci 2012; Regadas 2013; Tuncel 2010). All RCTs compared treatments in parallel design, except Bechara 2008, which used a cross-over design. The duration of studies varied from 30 days to 12 weeks. PDEIs used were not uniform across studies. Bechara 2008 used tadalafil 20 mg/d and Regadas 2013 5 mg/d, Tuncel 2010 used sildenafil 25 mg/4 times a week, and Gacci 2012 used vardenafil 10 mg/d. The AB used was uniform in type and dose across studies (tamsulosin 0.4 mg/d). Two of the four RCTs were placebo controlled and included a placebo arm along with the AB alone arm (Gacci 2012; Regadas 2013); the other two RCTs were not placebo controlled (Bechara 2008; Tuncel 2010). Two RCTs included a placebo run-in period (Bechara 2008; Gacci 2012), and the other two did not (Regadas 2013; Tuncel 2010). Participants included in Tuncel 2010 were treatment naïve, whereas remaining RCTs did not specify this.

PDEI + AB versus PDEI alone

Only one RCT, conducted in Turkey, was eligible for inclusion (Tuncel 2010). It included a total of 60 participants and three arms (sildenafil 25 mg four times a week vs tamsulosin 0.4 mg once a day vs sildenafil 25 mg four times a week + tamsulosin 0.4 mg per day). The duration of the study was eight weeks, and it included all treatment-naïve participants with both BPH-LUTS and ED. This study did not include a placebo run-in period, and participants directly entered the randomisation phase.

PDEI + 5-ARI versus 5-ARI alone

Only one study qualified for inclusion in this group (Casabe 2014). This study included 695 participants and was conducted in North America, Europe, and Latin America. The duration of the study was 26 weeks. Participants underwent a drug-free washout period of four weeks, followed by a four-week placebo run-in period, before randomisation. Participants were randomised to tadalafil 5 mg plus finasteride 5 mg per day or placebo plus finasteride 5 mg per day. Included participants had a larger prostate volume of 30 mL or greater and were naïve to 5-ARI therapy but not to other LUTS treatments, namely, alpha-blockers or anticholinergics.

PDEI + 5-ARI versus PDEI alone

We found no studies that met the inclusion criteria for this comparison.

PDEI + AB + 5-ARI versus AB + 5-ARI

We found no studies that met the inclusion criteria for this comparison.

Comparison of different PDEI agents for treatment of BPH-LUTS

We found no studies that met the inclusion criteria for this comparison.

Results of the search

We conducted the original search in May 2014 and updated the search through 20 February 2018. We have provided detailed results of the search in Figure 1.

Included studies

We included a total of 16 RCTs in the review. We have described the characteristics of included studies in the [Characteristics of included studies](#) section and in Table 1 and Table 2. We grouped studies by comparison. Some RCTs had more than two arms and hence were eligible for inclusion in more than one comparison group. Analysis of PDEI versus placebo included 11 RCTs; PDEI versus alpha-blockers four RCTs; combination of PDEI and AB versus AB alone four RCTs; combination of PDEI and alpha-blockers versus PDEI alone one RCT; and combination of PDEI and 5-ARI versus 5-ARI alone one RCT.

Excluded studies

We excluded RCTs not meeting the inclusion criteria for this review. We described the characteristics of excluded studies and reasons for exclusion in the [Characteristics of excluded studies](#) section.

Risk of bias in included studies

We have described below risk of bias assessment by comparison. We have presented in [Figure 2](#) a summary of this assessment.

PDEI versus placebo

Allocation (selection bias)

Random sequence generation

We judged seven of the 11 included RCTs as having unclear risk of bias ([Dmochowski 2010](#); [Kim 2011](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Yokoyama 2013](#)).

Allocation concealment

We judged nine of 11 RCTs as having unclear risk of bias ([Dmochowski 2010](#); [Gacci 2012](#); [Kim 2011](#); [McVary 2007a](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Yokoyama 2013](#)). Three RCTs used an interactive voice response system or opaque, sealed, and numbered envelopes; hence we rated them as having low risk of bias.

Blinding

Blinding of participants and personnel (performance bias)

We deemed risk of bias as unclear for six of 11 RCTs for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms ([Dmochowski 2010](#); [Kim 2011](#); [McVary 2007a](#); [McVary 2007b](#); [Porst 2011](#); [Yokoyama 2013](#)). However we judged AUR and need for surgical interventions as having low risk of bias for all included RCTs.

Blinding of outcome assessment (detection bias)

Risk of bias for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms was unclear for eight of 11 RCTs ([Dmochowski 2010](#); [Kim 2011](#); [McVary 2007a](#); [McVary 2007b](#); [Porst 2011](#); [Roehrborn 2008](#); [Stief 2008](#); [Yokoyama 2013](#)). However due to the nature of the outcomes of AUR and need for surgical intervention, we judged all included RCTs to have low risk of detection bias.

Incomplete outcome data (attrition bias)

Eight of 11 RCTs had unclear risk of bias for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms ([Dmochowski 2010](#); [Kim 2011](#); [McVary 2007a](#); [McVary 2007b](#); [Porst 2011](#); [Roehrborn 2008](#); [Stief 2008](#); [Yokoyama 2013](#)). Seven of 11 RCTs had unclear risk of bias for AUR and need for surgical interventions ([Dmochowski 2010](#); [Egerdie 2012](#); [McVary 2007a](#); [Oelke 2012](#); [Roehrborn 2008](#); [Stief 2008](#); [Yokoyama 2013](#)).

Selective reporting (reporting bias)

We judged one of the 11 included RCTs to have unclear risk of selective reporting bias for IPSS-total, BPHII, and IPSS-QOL ([Dmochowski 2010](#)). None of the included studies had selective reporting bias for AEs, treatment-related harms, AUR, or need for surgical intervention.

Other bias

We judged seven of the 11 included RCTs to have unclear risk of other bias for all outcomes because they used study designs that employed a placebo run-in period ([Egerdie 2012](#); [Kim 2011](#); [McVary 2007a](#); [McVary 2007b](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)).

PDEI versus alpha-blockers

Allocation (selection bias)

Random sequence generation

Three of the four included RCTs did not adequately describe the method used for random sequence generation; hence we judged them to have unclear risk of selection bias ([Kim 2011](#); [Tuncel 2010](#); [Yokoyama 2013](#)).

Allocation concealment

Three of the four included RCTs did not adequately describe the method used for allocation concealment; hence we judged them to have unclear risk of selection bias ([Kim 2011](#); [Tuncel 2010](#); [Yokoyama 2013](#)).

Blinding

Blinding of participants and personnel (performance bias)

We judged three of four RCTs to have unclear risk of performance bias for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms ([Kim 2011](#); [Tuncel 2010](#); [Yokoyama 2013](#)). We determined that none of the RCTs had performance bias for AUR or need for surgical intervention.

Blinding of outcome assessment (detection bias)

We judged three of four RCTs to have unclear risk of detection bias for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms ([Kim 2011](#); [Tuncel 2010](#); [Yokoyama 2013](#)). We determined that none of the RCTs had detection bias for AUR or need for surgical intervention.

Incomplete outcome data (attrition bias)

Two of four included RCTs had unclear risk of attrition bias for all outcomes ([Oelke 2012](#); [Yokoyama 2013](#)).

Selective reporting (reporting bias)

We judged all four included RCTs to have low risk of selective reporting bias for all outcomes.

Other bias

Three of four included RCTs employed placebo or an active drug run-in period before randomisation; hence we judged them to have unclear risk of other bias ([Kim 2011](#); [Oelke 2012](#); [Yokoyama 2013](#)).

PDEI + AB versus AB alone

Allocation (selection bias)

Random sequence generation

Three of the four included RCTs did not adequately describe the method used for random sequence generation; hence we judged them to have unclear risk of bias ([Bechara 2008](#); [Regadas 2013](#); [Tuncel 2010](#)).

Allocation concealment

No RCTs adequately described the method used; hence we judged them to have unclear risk of bias ([Bechara 2008](#); [Gacci 2012](#); [Regadas 2013](#); [Tuncel 2010](#)).

Blinding

Blinding of participants and personnel (performance bias)

We judged two of four RCTs to have unclear risk of performance bias for IPSS-total, BPHII, IPSS-QOL, AEs, and treatment-related harms (Regadas 2013; Tuncel 2010). We determined that no RCTs had performance bias for AUR or need for surgical intervention.

Blinding of outcome assessment (detection bias)

We judged two of four included RCTs to have unclear risk of bias (Regadas 2013; Tuncel 2010). However we determined that risk of detection bias was low for AUR and need for surgical interventions for all four studies, as they are less susceptible to such bias.

Incomplete outcome data (attrition bias)

We determined that none of the four RCTs had attrition bias for any outcomes.

Selective reporting (reporting bias)

We judged two of the four included studies to have unclear risk of selective reporting bias for quality of life assessments (BPHII and IPSS-QOL), AEs, and treatment-related harms (Gacci 2012; Regadas 2013). We determined that all four RCTs had low risk of bias for AE, AUR, and need for surgical intervention.

Other bias

We judged two of the four included RCTs to have unclear risk of other bias for all outcomes: one RCT because of lack of a washout period between two cross-over phases (Bechara 2008), and the other for including an active drug run-in period (Gacci 2012).

PDEI + alpha-blockers versus PDEI alone

We identified only one RCT for this comparison (Tuncel 2010).

Allocation (selection bias)

Random sequence generation

We judged this RCT to have unclear risk of selection bias for all outcomes because study authors did not describe the method used.

Allocation concealment

We judged risk of bias as unclear for allocation concealment for all outcomes.

Blinding

Blinding of participants and personnel (performance bias)

We judged the risk of performance bias as unclear for IPSS-total, BPHII, IPSS-QOL, and AE assessments, as study authors did not clearly describe whether participants and treatment administrators were masked to the interventions. However we judged the risk of performance bias to be low for AUR and need for surgical intervention, as they are less susceptible to such bias.

Blinding of outcome assessment (detection bias)

We judged the risk of detection bias as unclear for IPSS-total, BPHII, IPSS-QOL, and AE assessments, as study authors did not clearly describe whether outcome assessors were masked to the interventions. However we judged the risk of detection bias to be

low for AUR and need for surgical intervention, as they are less susceptible to such bias.

Incomplete outcome data (attrition bias)

We judged the risk of attrition bias to be low for all outcomes, as study authors reported no loss to follow-up and reported outcomes for all randomised participants.

Selective reporting (reporting bias)

We judged the risk of selective reporting bias to be low for all outcomes.

Other bias

We detected no significant risk of other bias.

PDEI + 5-ARI versus 5-ARI alone

We included only one RCT for this comparison (Casabe 2014).

Allocation (selection bias)

Random sequence generation

We judged this RCT to have unclear risk of bias.

Allocation concealment

Researchers used an interactive voice response system in allocating interventions to participants; therefore we judged allocation concealment to be adequate.

Blinding

Blinding of participants and personnel (performance bias)

We judged the risk of performance bias as unclear for IPSS-total, BPHII, IPSS-QOL, and AE assessments, as study authors did not clearly describe whether participants and treatment administrators were masked to the interventions. However we judged the risk of performance bias to be low for AUR and need for surgical intervention, as they are less susceptible to such bias.

Blinding of outcome assessment (detection bias)

We judged the risk of detection bias as unclear for IPSS-total, BPHII, IPSS-QOL, and AE assessments, as study authors did not clearly describe whether outcome assessors were masked to the interventions. However we judged the risk of detection bias to be low for AUR and need for surgical intervention, as they are less susceptible to such bias.

Incomplete outcome data (attrition bias)

This RCT had significant attrition of participants in both PDEI and combination groups. Therefore, we judged the risk of bias to be unclear for IPSS-total, BPHII, IPSS-QOL, AEs, AUR, and need for surgical intervention.

Selective reporting (reporting bias)

This study reported all relevant outcomes; hence we judged the risk of selective reporting bias to be low.

Other bias

Participants underwent a placebo run-in before randomisation. This may have led to selection of more compliant participants and hence may have compromised external validity. Therefore, we

judged the risk of bias to be unclear for IPSS-total, BPHII, IPSS-QOL, AEs, treatment-related harms, AUR, and need for surgical intervention.

Effects of interventions

See: [Summary of findings for the main comparison](#) PDEI compared to placebo for lower urinary tract symptoms consistent with benign prostatic hyperplasia; [Summary of findings 2](#) PDEI compared to alpha-blockers for LUTS associated with BPH; [Summary of findings 3](#) PDEI plus alpha-blocker compared to alpha-blockers alone for LUTS associated with BPH (short-term); [Summary of findings 4](#) PDEI plus an alpha-blocker compared to PDEI alone for LUTS associated with BPH (short-term); [Summary of findings 5](#) PDEI + 5-ARI compared to 5-ARI alone for LUTS associated with BPH (short-term); [Summary of findings 6](#) PDEI + 5-ARI compared to 5-ARI alone for LUTS associated with BPH (long-term)

PDEI versus placebo

Short-term (up to 12 weeks) efficacy and safety of PDEI compared to placebo

Eleven RCTs assessed the effects of PDEIs compared to placebo for short-term use (eight to 12 weeks).

Primary outcomes

IPSS-total score

PDEIs may result in a small improvement in IPSS (MD 1.89 lower, 95% CI 2.27 lower to 1.50 lower; 11 trials; low-quality evidence; [Analysis 1.1](#); [Figure 3](#) [Figure 4](#) [Summary of findings for the main comparison](#)). We downgraded the quality of evidence for study limitations and possible publication bias. The duration of treatment ranged from eight to 12 weeks. All included trials reported the mean change in IPSS-total score from baseline.

Figure 3. Forest plot of comparison: 1 PDEI versus placebo, outcome: 1.1 Change in IPSS-total: main analysis.

Figure 4. Funnel plot of comparison: 1 PDEI versus placebo, outcome: 1.1 Change in IPSS-total: main analysis.

BPHII score

PDEIs may result in a lower BPHII score (MD 0.52 lower, 95% CI 0.71 lower to 0.33 lower; eight trials; low-quality evidence; [Analysis](#)

1.6; [Figure 5](#); [Summary of findings for the main comparison](#)). We downgraded the quality of evidence for study limitations and imprecision, assuming an MCID of 0.5 ([Barry 1995](#)).

Figure 5. Forest plot of comparison: 1 PDEI versus placebo, outcome: 1.6 Change in BPHII: main analysis.

Adverse events

PDEIs may increase AEs (RR 1.42, 95% CI 1.21 to 1.67; 11 trials; low-quality evidence; [Analysis 1.10](#); [Figure 6](#); [Summary of findings for the main comparison](#)). This corresponds to 95 more AEs per

1000 men (95% CI 47 more to 151 more). We downgraded the quality of evidence for study limitations and clinically important inconsistency. We were concerned about possible publication bias but decided not to downgrade further.

Figure 6. Forest plot of comparison: 1 PDEI versus placebo, outcome: 1.10 Any AE with short-term use.

Secondary outcomes

IPSS-QOL score

PDEI probably results in a small improvement in IPSS-QOL (MD 0.26 lower, 95 CI 0.35 lower to 0.16 lower; nine trials; moderate-quality

evidence; [Analysis 1.15](#); [Figure 7](#)). We downgraded the quality of evidence for study limitations.

Figure 7. Change in IPSS-QOL with PDEI versus placebo

Acute urinary retention

Six of 11 RCTs did not report AUR. Reporting of AUR in five other RCTs was not uniform across PDEI and placebo groups (Egerdie 2012; Porst 2011; Roehrborn 2008; Takeda 2012; Yokoyama 2013). Egerdie 2012 reported no AUR observed in any of three treatment groups (tadalafil 2.5, 5 mg, and placebo). Porst 2011 reported no incidence of AUR in the tadalafil 5 mg treatment group, but they did not report the same for the placebo group. Roehrborn 2008 reported that one participant in the placebo group had AUR requiring catheterisation, but this RCT did not mention the incidence in any of the four tadalafil treatment groups. Takeda 2012 reported that one participant (74 years) in the tadalafil 5 mg group reported a severe adverse event (AUR) after 4.5 months of randomisation. This participant required catheterisation and had concomitant prostatitis. Yokoyama 2013 reported that one participant in the placebo group had urinary retention but did not mention the incidence in the tadalafil 2.5 and 5 mg groups.

Surgical interventions

None of the 11 RCTs, including 4386 participants in PDEI or placebo groups, reported the need for surgical intervention during the treatment period.

Other treatment-related harms

All included RCTs reported AEs as patient-reported safety outcomes. Treatment-related AEs most commonly reported were headache, flushing, dizziness, syncope, body pain, myalgia, back pain, nasopharyngitis, dyspepsia, epigastric discomfort, abdominal pain, and diarrhoea.

AEs related to vasodilatation (headache, flushing, dizziness, syncope, orthostatic hypotension, nasopharyngitis)

All 11 RCTs reported these AEs, although the extent of reporting varied. Researchers reported a total of 252 AEs related to vasodilatation in 2757 participants in the PDEI group and 115 in 1629 participants in the placebo group. The risk of AE due to vasodilatation was significantly higher in the PDEI group (RR 1.44, 95% CI 1.18 to 1.76; Table 3).

AEs related to body pain (myalgia, body pain, back pain, leg pain)

Ten of 11 RCTs (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Stief 2008; Takeda 2012; Yokoyama 2013) reported AEs related to body pain. Researchers reported a total of 107 AEs related to body pain in 2658 participants in the PDEI group and 15 in 1449 participants in the

placebo group. The RR of developing body pain was significantly higher with PDEI compared to placebo (RR 3.44, 95% CI 1.98 to 5.98; Table 3).

AEs related to GI tract (dyspepsia, gastroesophageal reflux disease (GERD), epigastric discomfort, abdominal pain, diarrhoea)

Eight of 11 RCTs reported AEs related to GI tract (Dmochowski 2010; Kim 2011; McVary 2007a; McVary 2007b; Oelke 2012; Roehrborn 2008; Stief 2008; Takeda 2012). The number of AEs related to the GI tract was 120 in 1884 participants treated with PDEI compared to 2 in 1111 participants treated with placebo. The RR of developing GI-related AEs was significantly higher with PDEIs compared to placebo (RR 14.19, 95% CI 5.80 to 34.72; Table 3).

Number of treatment discontinuations possibly due to AEs

Ten out of 11 RCTs (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007a; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn

2008; Takeda 2012; Yokoyama 2013) reported possible treatment discontinuation due to AEs. A total of 95 of 2649 participants in the PDEI group withdrew from treatment because of AEs, as did 21 of 1516 in the placebo group. The risk of treatment discontinuation due to AEs was higher in the PDEI group (RR 2.20, 95% CI 1.38 to 3.51; Table 3).

Subgroup analyses

In participants with or without ED

IPSS-total score

Data were available from five RCTs for participants with ED (MD -2.55, 95% CI -3.33 to -1.77; n = 1486) (Egerdie 2012; McVary 2007a; Oelke 2012; Porst 2011; Roehrborn 2008), and three RCTs provided data for participants without ED (MD -2.10, 95% CI -3.39 to -0.81; n = 330) (Oelke 2012; Porst 2011; Roehrborn 2008). The test for interaction was not significant (P = 0.56; Analysis 1.2; Figure 8).

Figure 8. IPSS-total subgroup analysis (PDEI vs placebo).

BPHII score

Data were available from five RCTs for participants with ED (MD -0.81, 95% CI -1.12 to -0.49; n = 1480) (Egerdie 2012; Oelke

2012; Porst 2011; Roehrborn 2008; McVary 2007a), and three RCTs provided data for participants without ED (MD -0.40, 95% CI -0.98 to 0.18; n = 329) (Oelke 2012; Porst 2011; Roehrborn 2008). The test for interaction was not significant (P = 0.23; Analysis 1.7; Figure 9).

Figure 9. Summary forest plot of subgroups for change in BPHII (PDEI Vs Placebo)

Adverse events

Data were available from four RCTs for participants with ED (McVary 2007a; Oelke 2012; Porst 2011; Roehrborn 2008), and three RCTs provided data for participants without ED (Oelke 2012; Porst 2011; Roehrborn 2008). The RR for AEs with PDEIs for participants with ED was 1.36 (95% CI 1.11 to 1.68; n = 1120), and the RR for AEs for participants without ED was 1.73 (95% CI 1.33 to 2.24; n = 338). The test for interaction was not significant (P = 0.16; Analysis 1.11; Figure 6).

Different PDEIs (tadalafil, sildenafil, vardenafil)

Nine of 11 RCTs compared tadalafil versus placebo (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Takeda 2012; Yokoyama 2013). One RCT used sildenafil (McVary 2007a), and one RCT used vardenafil (Stief 2008).

IPSS-total score

The MD for improvement in IPSS-total score for tadalafil was -1.80 (95% CI -2.20 to -1.39; n = 3738), for sildenafil -4.40 (95% CI -6.96 to -1.84; n = 341), and for vardenafil -2.20 (95% CI -3.57 to -0.83; n = 315). The test for interaction was not significant (P = 0.13; Analysis 1.3; Figure 9).

BPHII score

The MD for improvement in BPHII was -0.50 (95% CI -0.67 to -0.33; n = 3738; seven RCT) with tadalafil, and -1.10 (95% CI -2.11 to -0.09; n = 341; one RCT) with sildenafil. No data were available for vardenafil. The test for interaction was not significant (P = 0.25; Analysis 1.8; Figure 9).

Adverse events

The MD in the RR of any AE for tadalafil was 1.44 (95% CI 1.19 to 1.75; n = 3796; nine RCT), for sildenafil 1.22 (95% CI 0.99 to 1.51; n = 341), and for vardenafil 1.86 (95% CI 1.11 to 3.11; n = 315). The test for interaction was not significant (P = 0.25; Analysis 1.12; Figure 9).

Different doses of PDEIs

Nine RCTs compared tadalafil to placebo (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; Takeda 2012; Yokoyama 2013). Researchers administered tadalafil in doses of 2.5, 5, 10, or 20 mg daily; the most commonly used dose of tadalafil was 5 mg per day (seven of nine trials used this dose). Dmochowski 2010 used 20 mg daily, McVary 2007b used a dose escalation pattern starting with 5 mg and reaching up to 20 mg tadalafil but did not report the median dose used. McVary 2007a used sildenafil at a dose of 50 mg per day,

titrated to 100 mg per day for participants who could tolerate this. However, this study did not report the median dose of sildenafil. [Stief 2008](#) used vardenafil at a dose of 10 mg twice daily.

Study authors analysed dose-related effects only for tadalafil. Available data were insufficient for assessment of the same for sildenafil and vardenafil ([McVary 2007a](#); [Stief 2008](#)).

IPSS-total score

The MD for improvement in IPSS-total with tadalafil 2.5 mg/d was -1.31 (95% CI -2.19 to -0.42; n = 1396) ([Egerdie 2012](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)), with 5 mg/d -1.88 (95% CI -2.33 to -1.42; n = 2452) ([Egerdie 2012](#); [Kim 2011](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)), with 10 mg/d -3.43 (95% CI -4.79 to -2.07; n = 426) ([Roehrborn 2008](#)), and with 20 mg/d -3.29 (95% CI -4.44 to -2.14; n = 589) ([Dmochowski 2010](#); [Roehrborn 2008](#)). The test of interaction was significant (P = 0.008). Investigators observed a dose-dependent increase in improvement in IPSS-total score from 2.5 mg/d to 10 mg/d and observed the ceiling in effect size by increasing the dose up to 20 mg/d ([Analysis 1.4](#); [Figure 8](#)).

BPHII score

The MD for improvement in IPSS-total with tadalafil 2.5 mg/d was -0.28 (95% CI -0.61 to 0.04; n = 997) ([Egerdie 2012](#); [Roehrborn 2008](#); [Yokoyama 2013](#)), with 5 mg/d -0.47 (95% CI -0.70 to -0.25; n = 2139) ([Egerdie 2012](#); [Kim 2011](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)), with 10 mg/d -0.58 (95% CI -1.15 to -0.01; n = 426) ([Roehrborn 2008](#)), and with 20 mg/d -0.62 (95% CI -1.2 to -0.09) ([Dmochowski 2010](#); [Roehrborn 2008](#)). Researchers noted an indication of a dose-dependent improvement in BPHII for tadalafil from 2.5 mg/d through 20 mg/d; but the test for interaction was non-significant (P = 0.64; [Analysis 1.9](#); [Figure 9](#)).

Adverse events

The RR of any AE with tadalafil 2.5 mg/d was 1.23 (95% CI 1.03 to 1.46; n = 1405), with 5 mg/d 1.35 (95% CI 1.12 to 1.63; n = 2471), with 10 mg/d 1.63 (95% CI 1.19 to 2.24; n = 427), and with 20 mg/d 1.93 (95% CI 1.53 to 2.44; n = 620). The test for interaction was significant (P = 0.02), suggesting an increase in AE with increasing doses of tadalafil.

Sensitivity analyses

We conducted sensitivity analysis for RCTs with placebo or an active drug run-in period before the randomised intervention was provided. We included eight RCTs in the sensitivity analysis for reduction in IPSS-total ([Egerdie 2012](#); [Kim 2011](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)), and the MD between PDEI and placebo was similar to the main analysis (-1.84, 95% CI -2.30 to -1.39; n = 3567; [Analysis 1.5](#)).

We did not conduct a sensitivity analysis for BPHII, as it was the same as in the main analysis (all studies included a run-in period).

Sensitivity analysis for AEs included eight RCTs ([Egerdie 2012](#); [Kim 2011](#); [McVary 2007b](#); [Oelke 2012](#); [Porst 2011](#); [Roehrborn 2008](#); [Takeda 2012](#); [Yokoyama 2013](#)), and the RR of AEs with PDEIs versus placebo was similar to the main analysis (1.36, 95% CI 1.13 to 1.65; n = 3956; [Analysis 1.14](#)).

Overall, we detected no differences between the effect sizes obtained in sensitivity analyses and in the main analyses.

Long-term (up to one year) efficacy and safety of PDEI compared to placebo

The maximum duration of RCTs comparing PDEI to placebo was 12 weeks. No long-term comparative effectiveness data were available for any outcomes.

PDEI versus AB

Four RCTs comprising 936 participants compared PDEI monotherapy versus AB monotherapy ([Kim 2011](#); [Oelke 2012](#); [Tuncel 2010](#); [Yokoyama 2013](#)). Three RCTs used tadalafil, and one used sildenafil ([Tuncel 2010](#)). Duration of treatment ranged from eight to 12 weeks.

Short-term (up to 12 weeks) efficacy and safety of PDEI compared to AB

Primary outcomes

IPSS-total score

There is probably no difference between PDEI and AB for improvement in IPSS scores (MD 0.35 higher, 95% CI 0.28 lower to 0.98 higher; four trials; moderate-quality evidence; [Analysis 2.1](#); [Summary of findings 2](#)). We downgraded the quality of evidence for study limitations.

BPHII score

There may be no difference between PDEI and AB for improvement in BPHII scores (MD 0.03 higher, 95% CI 1.1 lower to 1.16 higher; two trials; low-quality evidence; [Analysis 2.5](#); [Summary of findings 2](#)). We downgraded the quality of evidence for study limitations and clinically important heterogeneity. We assumed the apparent imprecision to be secondary to observed inconsistency and did not downgrade further. Two trials with 403 participants reported this outcome ([Kim 2011](#); [Yokoyama 2013](#)).

Adverse events

Researchers most commonly reported AEs such as headache, myalgia, back pain, dizziness, dyspepsia, and nasopharyngitis. Trial results show 100 AEs reported in 397 participants on PDEIs compared to 79 AEs reported in 391 participants in the AB group. Rates of AEs may be similar (RR 1.35, 95% CI 0.80 to 2.30; four trials; low-quality evidence; [Analysis 2.9](#); [Summary of findings 2](#)). This corresponds to 71 more AEs per 100 men (95% CI 41 fewer to 264 more). We downgraded the quality of evidence for study limitations and clinically important inconsistency. We assumed the apparent imprecision to be secondary to observed inconsistency and did not downgrade further.

Secondary outcomes

IPSS-QOL score

PDEIs and ABs may have similar effects on IPSS-QOL (MD 0.1 lower, 95% CI 0.48 lower to 0.29 higher; four RCT; low-quality evidence; [Analysis 2.10](#)). We downgraded the quality of evidence for study limitations and clinically important heterogeneity.

Acute urinary retention

None of the four RCTs comprising 936 participants reported AUR as an event.

Surgical intervention

None of the four RCTs comprising 936 participants reported if there was any need for surgical intervention during the treatment period.

Other treatment-related harms

AEs related to vasodilatation

Researchers reported a total of 18 AEs related to vasodilatation in the PDEI group among 397 participants and seven AEs in the AB group among 391 participants. Risk of reporting vasodilatation-related AEs was significantly higher with tadalafil than with tamsulosin (RR 2.42, 95% CI 1.05 to 5.56; *n* = 746; [Analysis 2.14](#); [Table 4](#)).

AEs related to body pain

The number of AEs related to body pain was four among 378 participants treated with PDEIs compared to two among 369 participants treated with ABs. The risk of developing body pain was similar in PDEI and AB treatment groups (RR 1.75, 95% CI 0.38 to 8.18; *n* = 747; [Analysis 2.15](#); [Table 4](#)).

AEs related to GI tract

Three of the four RCTs reported AEs related to the upper GI tract (dyspepsia, GERD, epigastric discomfort, diarrhoea). The number of AEs related to the GI tract was four among 397 participants treated with PDEIs compared to zero among 389 participants treated with placebo. The odds of developing GI AEs were similar in PDEI and AB treatment groups (RR 4.87, 95% CI 0.58 to 41.22; *n* = 746; [Analysis 2.16](#); [Table 4](#)).

AEs leading to treatment discontinuation

A total of four of 397 participants in the PDEI group discontinued treatment compared to three of 391 in the AB group. The risk of treatment discontinuation was similar with PDEIs or ABs (RR 1.26, 95% CI 0.31 to 5.05; *n* = 786; [Analysis 2.17](#); [Table 4](#)).

Subgroup analyses

Participants with and without ED

[Tuncel 2010](#) enrolled participants with BPH-LUTS and ED. The MD obtained in this study was 1.40 (95% CI -2.24 to 5.04). The other studies included BPH-LUTS participants irrespective of their ED status. Therefore, data were insufficient for analysis of any outcomes.

Different PDEI

Results show appreciable heterogeneity among included RCTs with regard to doses of PDEI and AB used. Three RCTs used tadalafil 5 mg daily ([Kim 2011](#); [Oelke 2012](#); [Yokoyama 2013](#)), and one used sildenafil four times a week ([Tuncel 2010](#)). The dose of AB used was not uniform. [Oelke 2012](#) used 0.4 mg per day of tamsulosin, whereas [Kim 2011](#) and [Yokoyama 2013](#) used 0.2 mg per day of tamsulosin.

Results show no differences between tadalafil and tamsulosin treatment groups for IPSS-total (MD -0.13, 95% CI -0.65 to 0.91; *n* = 742) nor between sildenafil and tamsulosin groups (MD -1.40, 95% CI -2.24 to 5.04; *n* = 40; [Analysis 2.2](#)).

Findings show no differences between tadalafil and tamsulosin for BPHII (MD 0.23, 95% CI -0.23 to 0.69; *n* = 403; [Analysis 2.6](#)) nor for AE (RR 1.35, 95% CI 0.80 to 2.30; *n* = 742; [Analysis 2.9](#)).

Dose effects of PDEIs

Four comparison groups were available.

Tadalafil 5 mg per day versus tamsulosin 0.4 mg per day

We included only one RCT with 336 participants in this analysis ([Oelke 2012](#)). Results show no differences between tadalafil 5 mg/d and tamsulosin 0.4 mg/d treatment groups for improvement in IPSS-total (MD -0.60, 95% CI -1.98 to 0.78; *n* = 336; [Analysis 2.3](#)), BPHII (MD 0.24, 95% CI -0.40 to 0.88; *n* = 700; [Analysis 2.7](#)), and IPSS-QOL (MD -0.30, 95% CI -0.02 to 0.58; *n* = 336; [Analysis 2.12](#)).

Tadalafil 5 mg per day versus tamsulosin 0.2 mg per day

We included two RCTs in this comparison ([Kim 2011](#); [Yokoyama 2013](#)). Results show no differences between tadalafil 5 mg/d and tamsulosin 0.2 mg/d for improvement in IPSS-total (MD -0.42, 95% CI -0.68 to 1.51; *n* = 406; [Analysis 2.3](#)), BPHII (MD 0.04, 95% CI -1.13 to 1.21; *n* = 403; [Analysis 2.7](#)), AE (RR 2.41, 95% CI 0.51 to 11.50; *n* = 406; [Analysis 2.9](#)), and IPSS-QOL (MD 0.11, 95% CI -0.37 to 0.59; *n* = 406; [Analysis 2.12](#)).

Tadalafil 2.5 mg per day versus tamsulosin 0.2 mg per day

We included only one RCT in this analysis ([Yokoyama 2013](#)). Results show no differences between tadalafil 2.5 mg/d and tamsulosin 0.2 mg/d treatment groups for improvement in IPSS-total (MD -0.70, 95% CI -0.41 to 1.81; *n* = 303; [Analysis 2.3](#)), BPHII (MD 0.50, 95% CI -0.06 to 1.06; *n* = 297; [Analysis 2.7](#)), AE (RR 1.27, 95% CI 0.91 to 1.76; *n* = 306; [Analysis 2.9](#)), and IPSS-QOL (MD 0.30, 95% CI 0.02 to 0.58; *n* = 303; [Analysis 2.12](#)).

Sildenafil 25 mg 4 times a week versus tamsulosin 0.4 mg per day

We included only one RCT in this analysis ([Tuncel 2010](#)). Results show no differences between sildenafil 25 mg/d and tamsulosin 0.4 mg/d treatment groups for improvement in IPSS-total (MD -1.40, 95% CI -2.24 to 5.04; *n* = 40; [Analysis 2.3](#)) nor in IPSS-QOL (MD -0.80, 95% CI -1.78 to 0.18; *n* = 40; [Analysis 2.12](#)).

The dosages used across studies were not uniform, and the therapeutic equivalence status of dosages used is not clear. We maintained the standard tadalafil dose (5 mg/d) as a constant factor for comparison of groups 2 and 3, which suggests no differences in any outcome measures.

Sensitivity analyses for trials with run-in period

Sensitivity analysis included three trials ([Kim 2011](#); [Oelke 2012](#); [Yokoyama 2013](#)). Similar to the main analysis, results show no differences between PDEIs and ABs for IPSS-total (MD 0.07, 95% CI -0.88 to 1.02; *n* = 742; [Analysis 2.4](#)); BPHII (MD 0.03, 95% CI -1.10 to 1.16; *n* = 554; [Analysis 2.8](#); [Kim 2011](#); [Yokoyama 2013](#)), AEs (RR 1.35, 95% CI 0.80 to 2.30; *n* = 896), and IPSS-QOL (MD -0.01, 95% CI -0.38 to 0.36; *n* = 742; [Analysis 2.13](#)). We found no data for AUR and need for surgical intervention.

Long-term (up to one year) efficacy and safety of PDEIs compared to ABs

RCTs comparing PDEIs and ABs were 12 weeks in maximum duration. We found no available data for comparative long-term efficacy and safety of these two classes of drugs used for BPH-LUTS.

PDEI + AB versus AB alone

Four RCTs comprising 193 participants compared PDEI plus AB combination therapy versus AB monotherapy (Bechara 2008; Gacci 2012; Regadas 2013; Tuncel 2010). Two of these RCTs used tadalafil (Bechara 2008; Regadas 2013), one used sildenafil (Tuncel 2010), and one used vardenafil (Gacci 2012).

Short-term (up to 12 weeks) efficacy and safety of PDEI combination with AB compared to AB alone

Primary outcomes

IPSS-total

PDEI in combination with an AB may result in a small improvement in IPSS-total (MD 2.56 lower, 95% CI 3.92 lower to 1.19 lower; four trials, low-quality evidence; Analysis 3.1; Summary of findings 3), but we are unsure of this finding. We downgraded the quality of evidence for study limitations and clinically important imprecision, assuming an MCID of 3.

BPHII score

We could not assess this score because none of the four RCTs included BPHII as an outcome.

Adverse events

AE are probably increased when combination treatment is compared with AB alone (RR 2.81, 95% CI 1.53 to 5.17; four trials; moderate-quality evidence). We downgraded the quality of evidence for study limitations (Analysis 3.5; Summary of findings 3).

Secondary outcomes

IPSS-QOL score

Two of the four RCTs reported IPSS-QOL scores (Bechara 2008; Tuncel 2010), noting that combination therapy may improve IPSS-QOL scores slightly (MD -1.08, 95% CI -1.92 to -0.23; $n = 94$). The quality of evidence was low. We downgraded for study limitations and imprecision (Analysis 3.9).

Acute urinary retention

None of the four RCTs comprising 193 participants reported AUR as an event.

Surgical intervention

None of the four RCTs comprising 193 participants reported if there was any need for surgical intervention for any participants during conduct of the RCT.

Other treatment-related harms

AEs related to vasodilatation

Study authors reported a total of 27 AEs related to vasodilatation among 77 participants in the PDEI-AB combination group and four AEs among 77 participants in the AB alone group. Risk of vasodilatation-related AEs was higher with the combination treatment than with tamsulosin alone (RR 6.58, 95% CI 2.36 to 18.31; $n = 154$; Analysis 3.13; Table 5).

AEs related to body pain

None of the trials reported AEs related to body pain (Table 5).

AEs related to upper GI tract

Researchers reported a total of five AEs related to vasodilatation among 77 participants in the PDEI plus AB combination group and no AEs among 77 participants in the AB alone group. The risk of developing GI tract-related AEs was similar with PDEI and AB combination treatment compared to AB alone (RR 6.57, 95% CI 0.75 to 56.34; $n = 154$; Analysis 3.14; Table 5).

AEs leading to treatment discontinuation

One participant in the combination treatment group discontinued treatment compared to none in the AB only treatment. Differences between groups were not significant (RR 3.00, 95% CI 0.13 to 70.53; $n = 154$; Analysis 3.15; Table 5).

Subgroup analyses

Participants with and without ED

Tuncel 2010 enrolled participants with BPH-LUTS and ED. The other RCTs included BPH-LUTS participants irrespective of their ED status (Bechara 2008; Regadas 2013; Gacci 2012). However, these studies neither stratified participants based on the presence or absence of ED nor reported outcomes by this subgroup. Therefore, available study data were insufficient for meaningful analysis of any outcomes.

Different PDEIs

Bechara 2008 used tadalafil 20 mg/d and Regadas 2013 5 mg/d; Tuncel 2010 used sildenafil 25 mg 4 times/week, and Gacci 2012 used vardenafil 10 mg/d. All four RCTs used tamsulosin 0.4 mg/d as the AB for comparison. The test for interaction showed no differences between PDEI and tamsulosin combination groups versus tamsulosin alone ($P = 0.67$).

Dose effects of PDEIs

Researchers observed no dose effect for tadalafil (5 mg/d and 20 mg/d) in combination with tamsulosin (0.4 mg/d) versus tamsulosin (0.4 mg/d) alone ($P = 0.52$) for improvement in IPSS-total and AE. We could not assess the dose effect relationship for sildenafil and vardenafil, as available data were insufficient with only a single RCT for each (Analysis 3.3).

Sensitivity analysis

Of the four RCTs, two included a placebo run-in period for all participants included in the study preceding the randomisation phase, in addition to a drug for the washout period for participants who were previously treated and were not naïve to the study drug (Bechara 2008; Gacci 2012). The magnitude of improvement in IPSS-total was similar to findings in the main analysis (MD -2.34, 95% CI -4.02 to -0.66; $n = 114$; Analysis 3.4). The RR of AEs was found to be similar (MD 2.80, 95% CI 1.50 to 5.21; $n = 114$). Only one study reported improvement in IPSS-QOL with MD similar to the main analysis (-0.70, 95% CI -2.40 to 1.00; $n = 59$; Analysis 3.12; Bechara 2008).

Long-term (up to one year) efficacy and safety of PDEI combination with AB versus AB alone

None of the RCT continued beyond 12 weeks; therefore no data are available for assessing the long-term efficacy and safety of the combination of PDEI and AB versus AB alone for BPH-LUTS.

PDEI + AB versus PDEI alone

Only one RCTs qualified for this comparison, with three intervention arms: tamsulosin 0.4 mg daily (n = 20), sildenafil 50 mg four times weekly plus tamsulosin 0.4 mg daily (n = 20), and sildenafil 50 mg four times weekly ([Tuncel 2010](#)). For analysis, we included group data from two arms comprising only 40 participants. The duration of the study was eight weeks, and all participants were naïve to the study drugs.

Short-term (up to 12 weeks) efficacy and safety of PDEI combination with AB compared to PDEI alone

Primary outcomes

IPSS-total score

PDEI in combination with an AB may result in small improvement in IPSS-total compared to PDEI alone (MD 2.4 lower, 95% CI 6.47 lower to 1.67 higher; one trial; low-quality evidence; [Analysis 4.1; Summary of findings 4](#)). We downgraded the quality of evidence for study limitations and clinically important imprecision, assuming an MCID of 3.

BPHII score

[Tuncel 2010](#), did not report this outcome.

Adverse events

[Tuncel 2010](#) reported no withdrawals due to AEs but did not report whether any AEs occurred.

Secondary outcomes

IPSS-QOL score

PDEI in combination with an AB may result in similar improvement in IPSS-QOL (MD 0.4 lower, 95% CI 1.8 lower to 1.0 higher; one trial; low-quality evidence) compared to PDEI alone. We downgraded for study limitations and clinically important imprecision, assuming an MCID of 0.5.

Acute urinary retention

[Tuncel 2010](#) did not report this outcome.

Surgical intervention

[Tuncel 2010](#) also did not report this outcome.

Subgroup analyses

We conducted no subgroup analyses, as the sample size was small and researchers did not report outcomes as per the subgroups.

Sensitivity analysis

We performed no sensitivity analysis, as we included only one study for this comparison.

Long-term (up to one year) efficacy and safety of PDEI combination with AB compared to PDEI alone

For this comparison, we identified only one RCT that was eight weeks in duration. No other long-term data were available for this analysis. Hence the evidence is insufficient to determine comparative long-term efficacy and safety of the PDEI combination with AB versus AB alone.

PDEI + 5-ARI versus 5-ARI alone

Short-term (up to 12 weeks) efficacy and safety of PDEI combination with 5-ARI compared to 5-ARI alone

Only one RCT qualified for inclusion in this analysis ([Casabe 2014](#)). This study compared tadalafil 5 mg plus finasteride 5 mg daily (n = 345) versus placebo plus finasteride 5 mg daily (n = 350) in a parallel-group design. All participants were naïve to finasteride therapy. They underwent a four-week drug-free washout period followed by a four-week placebo run-in period before enrolment. The study was 26 weeks in duration. Study authors assessed the efficacy of treatments for IPSS-total score at four, 12, and 26 weeks.

Primary outcomes

IPSS-total score

PDEI in combination with a 5-ARI is likely to result in a small improvement in IPSS (MD 1.4 lower, 95% CI 2.84 lower to 1.16 lower; one RCT; moderate-quality evidence) at 12 weeks. We downgraded for study limitations.

BPHII score

The only study identified for this comparison did not evaluate BPHII scores; hence we found no data pertaining to this outcome ([Casabe 2014](#)).

Adverse events

[Casabe 2014](#) did not report AEs at 12 weeks.

Secondary outcomes

IPSS-QOL score

PDEI plus 5-ARI probably has a similar effect on IPSS-QOL (MD 0.2 lower, 95% CI 0.48 lower to 0.06 lower; one RCT; moderate-quality evidence) at 12 weeks compared to 5-ARI alone. We downgraded the quality of evidence for study limitations.

Acute urinary retention

[Casabe 2014](#) did not report AUR as an event during the study in either of the treatment groups at 12 weeks.

Surgical intervention

[Casabe 2014](#) also did not report if there was any need for surgical intervention for any participants at 12 weeks during conduct of the RCT.

Long-term (up to one year) efficacy and safety of PDEI combination with 5-ARI compared to 5-ARI alone

Primary outcomes

IPSS-total

The combination of PDEI and 5-ARI probably leads to minor improvement in IPSS-total (MD 1.0 lower, 95% CI 1.84 lower to 0.86 lower; one trial; moderate-quality evidence) compared to 5-ARI alone after 24 weeks of treatment. We downgraded the quality of evidence for study limitations.

BPHII score

The only study identified for this comparison did not evaluate BPHII scores; hence we found no data pertaining to this outcome ([Casabe 2014](#)).

Adverse events

AEs may be similar in the long term (RR 1.07, 95% CI 0.84 to 1.36; one trial; low-quality evidence). This corresponds to 19 more AEs per 1000 men (95% CI 43 fewer to 98 more). We downgraded the quality of evidence for study limitations and clinically important imprecision.

Secondary outcomes

IPSS-QOL score

The combination of PDEI and 5-ARI probably improves IPSS-QOL to a small degree (MD 0.2 lower, 95% CI 0.48 lower to 0.08 lower; one trial; moderate-quality evidence) at 24 weeks compared to 5-ARI alone. We downgraded the quality of evidence for study limitations.

Acute urinary retention

Casabe 2014 did not report AUR as an event during the study in either treatment group.

Surgical intervention

Casabe 2014 also did not report if there was any need for surgical intervention for any participants during conduct of the RCT.

Subgroup analyses

We were unable to conduct any of the preplanned subgroup analyses, as no data were available.

Sensitivity analysis

We did not perform the sensitivity analyses, as we identified only a single RCT for this comparison.

Other treatment-related harms

Results show a higher number of body pain-related AEs (RR 2.70, 95% CI 1.07 to 6.81) in the combination treatment group (Analysis 5.5), but show no difference in AEs related to vasodilatation (RR 1.01, 95% CI 0.46 to 2.22), upper GI symptoms (RR 4.05, 95% CI 0.87 to 18.92), and treatment discontinuation (RR 0.63, 95% CI 0.21 to 1.91) between groups (Analysis 5.4; Analysis 5.6; Analysis 5.7). Data also show no difference in AEs related to sexual function (RR 0.51, 95% CI 0.17 to 1.4) between the finasteride and tadalafil combination group and the finasteride and placebo group (Analysis 5.8; Table 6).

DISCUSSION

Summary of main results

We found data from eligible randomised controlled trials (RCTs) to conduct analysis of five comparisons, with data largely limited to a short time horizon of 12 weeks of treatment. The preponderance of evidence pertains to the use of phosphodiesterase inhibitors (PDEIs) compared to placebo.

Compared to placebo, PDEIs probably improve International Prostate Symptom Score (IPSS)-total slightly over placebo with short-term use over six to 12 weeks. They may also slightly improve quality of life (QOL) and may lead to increased rates of adverse events (AEs). We found no long-term data on treatment beyond 12 weeks.

Use of PDEIs and alpha-blockers (ABs) in benign prostatic hyperplasia (BPH) probably provides similar improvement in IPSS-

total score and may lead to similar improvement in QOL. The incidence of AEs may be similar. We found no long-term data on treatment beyond 12 weeks.

The PDEI and AB combination may provide a small improvement in IPSS-total score compared to either drug alone. We found no data on the Benign Prostatic Hyperplasia Impact Index (BPHII) nor on AEs. Effects on IPSS-QOL may be similar. All study results were limited to treatment duration of four to 12 weeks.

For short-term use (up to 12 weeks), the combination of a PDEI and a 5-alpha reductase inhibitor (5-ARI) probably results in a very small improvement in IPSS-total score compared to 5-ARI alone. We found no evidence on BPHII scores or AEs. Effects on IPSS-QOL are likely similar. With long-term (13 to 26 weeks) use, the combination of PDEI and 5-ARI likely results in a very small reduction in IPSS-total score. We found no evidence about its effects on BPHII scores. There may be no difference in the rate of AEs, and effects on IPSS-QOL are likely similar.

Overall completeness and applicability of evidence

We included 16 randomised controlled trials (RCTs) that address five comparisons. Limitations are as follows.

- Most studies were short-duration efficacy studies (maximum of 12 weeks) and did not provide longer-term data. This issue is relevant in that lower urinary tract symptoms (LUTS) typically are chronic in nature and medications are typically used for years.
- This review focused on the most patient-important outcomes that could meaningfully be assessed in RCTs. We did not include non-randomised studies, which are considered important for assessing long-term and rare outcomes. Emerging evidence indicates that long-term use of phosphodiesterase (PDE) may increase the risk of melanoma (Deng 2018; Feng 2018; Han 2018; Li 2014; Lian 2016; Loeb 2015; Loeb 2017; Matthews 2016; Pottegard 2016; Tang 2017; Wrishko 2009; Wronski 2014), but this topic is outside the scope of this review.
- More than 80% of study participants (8/11 RCTs) were men of Caucasian origin; 4% to 6% were black, and 8% to 11% were of Asian ethnicity (in three RCTs that recruited mainly in Japan and Korea). Outcomes for men of other ethnic backgrounds may differ.

Quality of the evidence

Despite a large number of RCTs across the five analysed comparisons, we found no high-quality evidence for any outcome. The quality of evidence ranged mostly from moderate to low, with low-quality evidence representing the most frequent category. The most common reasons for downgrading quality were study limitations, although we did not rate any domain as having high risk of bias; there was a preponderance of unclear risk of bias related to selection, performance, detection, and sometimes selective reporting bias, which in aggregate prompted us to downgrade by one level. Other reasons for downgrading were clinically important imprecision (when the minimal clinically important difference (MCID) or other assumed threshold of clinical relevance was crossed) and funnel plot asymmetry, raising concerns about publication bias. Overall, this indicates that our confidence in most effect estimates is limited; the true effect may be close to or substantially different from the reported estimate of the effect.

Potential biases in the review process

During the conduct of the review, we made several conscious deviations from the protocol with regards to inclusion of only RCTs that reported some use of blinding, and dropping of some secondary outcomes and preplanned subgroup analyses. We made these modifications to reduce the length of the review, to improve readability, and to focus on aspects that are most important for clinical practice. We believe that this is unlikely to have introduced bias into the process of conducting this systematic review.

We conducted an extensive literature search and updated the search from time to time during conduct of the review. Although focus on the English language could be a potential limitation, we also looked for studies registered at ClinicalTrials.gov and the World Health Organization (WHO) clinical trial registries to identify potentially eligible studies. Therefore, it is unlikely that the review process would have been biased by missing studies. We noted certain limitations during the review process, such as the challenge of excluding non-English language studies and grey literature from the review due to incomplete identification of these studies. However, this is a generic limitation associated with systematic reviews. Another limitation involved the detection of serious and/or rare AEs. This review included only RCTs, and review authors excluded other non-randomised studies. This jeopardises the scope for comprehensive detection of AEs encountered in population-based studies. The shorter duration of the included studies also contributes to non-detection of long-term usage-related AEs.

This review includes data from the included RCTs and notes that some information is missing from some of the included studies. Upon repeated attempts to obtain missing data from one RCT (Tamimi 2010), we failed. Nevertheless, this may not have affected the effect size of estimates, as we included data for 11 of the 12 RCTs in the primary analysis.

Agreements and disagreements with other studies or reviews

Several systematic and descriptive (narrative) reviews have been published in recent years on the efficacy and clinical use of PDEIs (specifically tadalafil) for BPH-LUTS. These reviews have far outnumbered the original studies conducted over the last decade (Alsaikhan 2014; Anderson 2007; Brock 2014; Fullhase 2014; Gacci 2011; Govorov 2014; Guliano 2012; Hatzimouratidis 2014; Jiang 2013; Martinez-Salamanca 2011; Miller 2013; Radomski 2014; Rosso 2015; Silva 2014; Wronski 2014; Ukcet 2013; Yan 2014), with many of them recommending PDEI treatment for BPH-LUTS, and a few expressing skepticism about this treatment. Meanwhile, it is not the intent of this review to make any recommendations about appropriate clinical use.

A total of four meta-analyses had been conducted to review the evidence showing effects of PDEIs versus placebo for BPH-LUTS.

- The earliest systematic review - Laydner 2011 - included four RCTs (McVary 2007a; McVary 2007b; Roehrborn 2008; Stief 2008; n = 1880). This was only a narrative analysis, and review authors stated that a meta-analysis could not be conducted because of heterogeneity issues. (However, we did not find statistical heterogeneity when analysing the data ourselves; $I^2 = 21\%$.) Review authors concluded that PDEIs are useful in BPH-LUTS to improve LUTS, erectile function, and quality

of life. They conducted no meta-analysis, and review authors were closely associated with the drug development process and initial clinical testing.

- Another systematic review - Liu 2011 - included five RCTs (Dmochowski 2010; McVary 2007a; McVary 2007b; Roehrborn 2008; Stief 2008, n = 2074) out of which four RCTs compared tadalafil to placebo (Dmochowski 2010; McVary 2007b; Roehrborn 2008; Stief 2008). This systematic review reported the MD for IPSS-total as -2.57 (95% CI -3.15 to -1.98) for tadalafil and had methodological deficiencies with regard to its conduct. An issue arose regarding "unit of analysis" because the placebo group was included four times, spuriously increasing the sample size and hence compromising the accuracy of the estimates. Corrected analysis showed MD of -2.29 (95% CI -2.91 to -1.68). The effect size obtained in our study on a larger sample size (11 RCTs; n = 4293) was less than that noted in this analysis (-1.80 vs -2.57).
- Gacci 2012 b was a systematic review that included data from four clinical trials (McVary 2007a; McVary 2007b; Roehrborn 2008; Stief 2008; Tamimi 2010; n = 2749). The MD in IPSS-total improvement with PDEI over placebo reported in this study was -2.8 (95% CI -3.6 to -2.1), whereas our analysis of a larger participant population revealed an MD of -1.89 (95% CI -2.28 to -1.64; n = 4293).
- The fourth systematic review meta-analysis - Dong 2013 - included seven RCTs using tadalafil or placebo (Dmochowski 2010; Egerdie 2012; Kim 2011; McVary 2007b; Oelke 2012; Porst 2011; Roehrborn 2008; n = 2913). The mean effect size on IPSS-total was found to be -2.35 (95% CI -2.83 to -1.88). A larger participant pool in our study showed a smaller effect size.

Meanwhile, our review stands out on the basis of its methodological rigor, which includes a published, a priori protocol; a comprehensive literature search of the published and unpublished literature, irrespective of language of publication; the use of GRADE on a per-outcome basis; and a focus on patient-important outcomes and clinically important differences. We also would like to emphasise the strict conflict of interest policy of Cochrane, to which we adhered, whereas many other reviews have been published by review authors with recognised financial and/or intellectual conflicts of interest.

AUTHORS' CONCLUSIONS

Implications for practice

Current best evidence suggests that a PDEI (tadalafil) used for treatment of BPH-LUTS over a short period of 12 weeks provides a relatively very small improvement in urinary symptoms and quality of life compared to placebo at the cost of increased risk of AEs. The available body of evidence lacks information on whether such modest improvement can be maintained for longer periods as compared with an AB. The nature and incidence of long-term AEs with PDEIs are not well known.

The efficacy and safety of PDEIs may be similar to ABs for BPH-LUTS. However, our confidence in these estimates is low.

PDEI combined with AB does not appear to add benefit for improvement of urinary symptoms, but it may result in a minor improvement when combined with 5-ARI in men with a larger prostate.

Implications for research

We found evidence of moderate to low quality for the efficacy and safety outcomes with short-term use of a PDEI (tadalafil) in men with BPH-LUTS. We frequently downgraded for issues such as study limitations, inconsistency, clinically important imprecision, and heterogeneity, although not for publication bias. Future trials should be conducted with greater methodological rigor and must be published irrespective of the direction of their findings. In addition, they must be adequately powered, must be stratified to permit meaningful subgroup analyses, and must evaluate drugs for longer periods to assess their efficacy as well as safety.

In eight of 11 RCTs included in this systematic review, the placebo group successfully met the [AUA 2010](#) definition of minimum clinically important difference (MCID), improving urinary symptoms by more than 3 points on the IPSS-total scale (single best and universally accepted outcome measure for evaluation and treatment of urinary symptoms in BPH). Therefore, technically, this fulfilled the AUA criteria for an effective intervention for BPH-

LUTS. Robust placebo response based on IPSS-total scores merits consideration of revision of the MCID for BPH-LUTS. The MCID for BPH-LUTS was proposed more than two decades back ([Barry 1995](#)), and it has been endorsed by the AUA. Further research may be needed to set new MCID criteria, which should take into account the extent of placebo response.

With emerging concerns about use of PDEIs and the incidence of melanoma ([Deng 2018](#); [Feng 2018](#); [Han 2018](#); [Lian 2016](#); [Loeb 2015](#); [Loeb 2017](#); [Matthews 2016](#); [Pottgard 2016](#); [Tang 2017](#); [Wang 2017](#); [Wronski 2014](#)), studies tracking the long-term health outcomes of PDEI users to assess for rare yet serious AEs are important. Longitudinal studies and drug-specific registries should be considered, as RCTs are unlikely to be of adequate power or duration to detect such AEs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bechara 2008

Methods	Study design: randomised double-blind cross-over study Setting: single centre Duration of the study: September 2007 to February 2008
Participants	Inclusion criteria: men who are 50 years old, clinical diagnosis of BPH by medical history and physical examination (including digital rectal examination), IPSS 12 points at baseline, total serum prostate-specific antigen (PSA) 4.0 ng/mL, Qmax > 5 mL/s and < 15 mL/s with minimum voided volume > 125 mL at screening, willing and able to give written informed consent and to comply with study procedures Exclusion criteria: total serum PSA > 4 ng/mL; history or evidence of prostate cancer; previous prostatic surgery or other invasive procedure to treat BPH; post-void residual volume (PVR) > 250 mL (suprapubic ultrasound) at screening; history of acute urinary retention (AUR) within 3 months before screening visit; any causes other than BPH that may in the judgement of the investigator result in urinary symptoms or changes in flow rate (i.e. neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infections); use of any 5-ARI or use of phytotherapy within 6 months before screening visit; use of any alpha-adrenoreceptor blockers within 2 weeks of screening visit; use of any PDE ₅ inhibitors within 2 weeks of screening visit; cer-

Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia (Review)

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Bechara 2008 (Continued)

tain cardiovascular diseases, for example, unstable angina, recent myocardial infarction, or poorly controlled blood pressure; clinically significant renal or hepatic insufficiency; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens, or a potent cytochrome P450 3A4 inhibitor; or uncontrolled diabetes (glycosylated HbA1c > 9%)

Total number of participants: 30

Intervention: n = 15, control: n = 15

Age: 63.7 (51 to 78) years

IPSS-total: 19.4 (12 to 34)

Interventions	<p>Intervention(s): tadalafil 20 mg/d + tamsulosin 0.4 mg/d (n = 15)</p> <p>Control(s): tamsulosin 0.4 mg/d + placebo (n = 15)</p> <p>Run-in-period: 2-week medication-free run-in period</p> <p>Duration: 45 days each period, cross-over</p>
Outcomes	<p>Primary efficacy: IPSS-total, IPSS-QOL, Qmax, PVR, global assessment questionnaire (GAQ)</p> <p>Secondary efficacy: IIEF-EF, sexual encounter profile (SEP)-Q2, SEP-Q3</p> <p>Safety measure: patient-reported adverse events, changes in vital signs</p>
Notes	Funding sources are not mentioned and conflicts of interest have been declared as none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized"</p> <p>Comment: the process of random sequence generation is not described</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized, double blind, cross-over study"</p> <p>Comment: the process of allocation concealment is not described</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	<p>Quote: "in order to assure double-blind procedures, all the capsules were identical and prepared by a third party (pharmacist) in numbered containers. Placebo drugs and tadalafil drug were prepared as identical capsules.Neither the patient nor the investigator knew which drug they were receiving"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	<p>Quote: "in order to assure double-blind procedures, all the capsules were identical and prepared by a third party (pharmacist) in numbered containers. Placebo drugs and tadalafil drug were prepared as identical capsules.Neither the patient nor the investigator knew which drug they were receiving"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	<p>Quote: "in order to assure double-blind procedures, all the capsules were identical and prepared by a third party (pharmacist) in numbered containers. Placebo drugs and tadalafil drug were prepared as identical capsules.Neither the patient nor the investigator knew which drug they were receiving"</p> <p>Comment: the risk of bias is low</p>

Bechara 2008 (Continued)

Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "neither the patient nor the investigator knew which drug they were receiving" Comment: the risk of bias appears to be low
Blinding of outcome assessment (detection bias) AE and treatment related harms	Low risk	Quote: "neither the patient nor the investigator knew which drug they were receiving" Comment: the risk of bias appears to be low for adverse event assessments
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "neither the patient nor the investigator knew which drug they were receiving" Comment: the risk of bias appears to be low
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 27 of 30 participants (95%) in tamsulosin + tadalafil group and 27 of 30 (95%) in tamsulosin + placebo group completed the study; outcomes have been reported for them Comment: the risk of bias appears to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 27 of 30 participants (95%) in tamsulosin + tadalafil group and 27 of 30 (95%) in tamsulosin + placebo group completed the study; adverse events have been reported for them Comment: the risk of bias appears to be low
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: 27 of 30 participants (95%) in tamsulosin + tadalafil group and 27 of 30 (95%) in tamsulosin + placebo group completed the study. There are no reports of acute urinary retention and need for surgical intervention in either study group during any study period Comment: the risk of bias appears to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: no protocol was available for this study. Relevant outcomes have been reported. The risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no protocol was available for this study. Adverse events have been reported. The risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no protocol was available for this study. Risk of bias appears to be low as these events are unlikely to be missed
other bias All outcomes	Unclear risk	Comment: there was no washout period between the 2 cross-over periods. Therefore, the risk of bias for all outcomes appears to be unclear

Brock 2013a

Methods Post hoc integrated analysis of 3 studies with similar design

Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia (Review)

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Brock 2013a (Continued)

Roherborn 2008: randomised double-blind placebo controlled parallel-design dose-finding 12-week study

Prost 2011: randomised double-blind placebo-controlled parallel-design 12-week study

Oelke 2012: double-blind placebo- and active-controlled parallel-design 12-week study

Participants	<p>Roherborn 2011: men > 45 years, BPH-LUTS > 6 months, IPSS > 13, Qmax 4 to 15 mL/s, PVR for entering the placebo lead-in period</p> <p>Prost 2011: men > 45 years, BPH-LUTS > 6 months, IPSS > 13, Qmax 4 to 15 mL/s for entering the placebo lead-in period</p> <p>Oelke 2012: men ≥ 45 years, BPH-LUTS > 6 months, IPSS ≥ 13, Qmax 4 to 15 mL/s before placebo lead-in period</p>
Interventions	Tadalafil 5 mg/d (n (participants with ED) = 167), (n (participants without ED) = 377) vs placebo (n (participants with ED) = 171), (n (participants without ED) = 374)
Outcomes	<p>Primary: IPSS-total</p> <p>Secondary: IIEF, IPSS-storage, IPSS-voiding, Qmax, PVR, BPHII</p>
Notes	Data for participants with ED or without ED were analysed only for 5 mg/d dose of tadalafil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized" (Roehrborn 2008); "randomized" (Prost 2011); "randomization was stratified..." (Oelke 2012)</p> <p>Comment: probably done; the method used for random sequence generation is not described in adequate detail in the contributing studies</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized, double-blind" (Roehrborn 2008); "randomization was stratified....." (Oelke 2012); "randomized, double-blind" (Prost 2011)</p> <p>Comment: probably done; the procedure adopted for allocation concealment is not described in adequate detail in the method sections of the contributing studies</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	<p>Quote: "double-blind" (Roehrborn 2008); "double blind" (Prost 2011); "double blind" (Oelke 2012)</p> <p>Comment: probably done; however in the contributing studies, who was blinded is not described in adequate detail</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	<p>Quote: "double-blind" (Roehrborn 2008); "double blind" (Prost 2011); "double blind" (Oelke 2012)</p> <p>Comment: probably done; however in the contributing studies, who was blinded is not described in adequate detail</p>
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	<p>Quote: "double-blind" (Roehrborn 2008); "double blind" (Prost 2011); "double blind" (Oelke 2012)</p> <p>Comment: probably done; the contributing studies do not describe in adequate detail who was blinded. However, these outcomes are objective and risk of bias appears to be low, as they are not susceptible to performance bias</p>

Brock 2013a (Continued)

Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" (Oelke 2012) Quote: "double blind" (Prost 2011); randomized, double-blind, placebo-controlled" (Roehrborn 2008) Comment: probably done; however in the contributing studies, whether outcome assessors were blinded is not described in adequate detail. Therefore, the risk of bias appears to be unclear for these outcomes
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double-blind" (Roehrborn 2008); "double blind" (Prost 2011); "double blind" (Oelke 2012) Comment: probably done; however in the contributing studies, whether outcome assessors were blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind" (Roehrborn 2008); "double blind" (Prost 2011); "double blind" (Oelke 2012) Comment: probably done; in the contributing studies, whether outcome assessors were blinded is not described in adequate detail. However, these outcomes are objective and are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	IPSS-total reported for 163/163 (100%) men without ED; 373/373 (100%) men with ED in tadalafil 5 mg/d group and 63/163 (100%) men without ED; 369/369 (100%) men with ED in placebo group BPHII reported for 163/163 (100%) men without ED; 367/367 (100%) men with ED in tadalafil 5 mg/d group and 166/166 (100%) men without ED; 367/367 (100%) men with ED in placebo group IPSS-QOL reported for 163/163 (100%) men without ED; 373/373 (100%) men with ED in tadalafil 5 mg/d group and 167/167 (100%) men without ED; men 372/372 (100%) men with ED in placebo group Outcomes were reported for participants in intervention (100%) and control (100%) arms for IPSS-total, BPHII, and IPSS-QOL
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Adverse events reported for 163/163 (100%) men without ED; 373/373 (100%) men with ED in tadalafil 5 mg/d group and 167/167 (100%) men without ED; men with ED 372/372 (100%) in placebo group Therefore, the risk of bias appears to be low
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Trial authors have not reported adverse events related to urinary retention in both tadalafil 5 mg/d (544) and placebo (545) groups. However, these outcomes are objective; therefore, the risk of bias appears to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	The risk appears to be low for these outcomes
Selective reporting (reporting bias) AE and treatment related harms	Low risk	The risk appears to be low for these outcomes
Selective reporting (reporting bias)	Low risk	These outcomes were not reported for participants in the intervention or control arm. However, the risk appears to be low for these outcomes

Brock 2013a (Continued)

Acute urinary retention
and need for surgical in-
tervention

other bias All outcomes	Unclear risk	Potential risk of bias due to the placebo run-in period cannot be ruled out, as it will enrich the study population with those who are more compliant
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Casabe 2014

Methods	Study design: randomised double-blind parallel-group study Setting: multi-centric Duration of the study: November 2010 to September 2012
Participants	Inclusion criteria: men 45 years of age or older with BPH-LUTS for longer than 6 months; prostate volume ≥ 30 mL (confirmed via transrectal ultrasound); IPSS-total score ≥ 13 and Qmax 4 to 15 mL/s; and naïve to 5-ARI therapy Exclusion criteria: none specified Total number of participants randomly assigned: 696 Mean Age: 63.7 (range 46 to 86) years Mean IPSS-total: 17.3 (SD = 5.7)
Interventions	Intervention(s): tadalafil 5 mg + finasteride 5 mg per day (n = 350) Control(s): placebo + finasteride 5 mg per day (n = 345) Run-in period: 4-week washout period followed by 4-week placebo run-in period Duration of study interventions: 12 weeks (for primary endpoint) Study continued maintaining blinding for secondary endpoints until 26 weeks
Outcomes	Primary efficacy: IPSS-total at 12 weeks Secondary efficacy: IPSS-storage; IPSS-voiding; IPSS-QOL; IPSS-nocturia; erectile function domain of the IIEF-EF20 after 4, 12, and 26 weeks of therapy in men who were sexually active and had ED at baseline; PGI-I (Patient Global Impression of Improvement) and CGI-I (Clinician Global Impression of Improvement) after 26 weeks (or endpoint) of therapy Safety assessments: participant reported treatment-related adverse events (TEAEs), serious adverse events (SAEs), vital signs, and clinical laboratory values
Notes	The funding source for the study has not been stated in the published manuscript. Eight of nine authors have declared financial interest and/or other relationships with Eli Lilly the manufacturer of the study drug tadalafil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described

Casabe 2014 (Continued)

Allocation concealment (selection bias) All outcomes	Low risk	Quote: "interactive voice response system (IVRS) was used to allocate patients to treatment groups" Comment: the process of allocation concealment appears adequate
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" Comment: who was masked to the interventions is not described in adequate detail
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: who was masked to the interventions is not described in adequate detail
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: who was masked to the interventions is not described in adequate detail; however, these outcomes are objective and are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" Comment: whether treatment administrator or assessor was blinded is not described; therefore, the risk of bias appears to be unclear
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: whether treatment administrator or assessor was blinded is not described in adequate detail; therefore, the risk of bias appears to be unclear
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: whether treatment administrator or assessor was blinded is not described in adequate detail; however these outcomes are objective in nature and are less susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 306/345 (88.4%) participants in tadalafil + finasteride group and 286/350 (81.7%) in placebo + finasteride group completed the 26-week treatment period. The number of participants whom IPSS-total and IPSS-QOL are reported is not mentioned. The risk of bias appears to be unclear
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: adverse events were reported for 345/345 participants in tadalafil + finasteride group and for 350/350 participants in placebo + finasteride group at 26 weeks of treatment. However, the risk of bias appears to be unclear, as only 88.4% and 81.4% of participants completed the study
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: safety reporting was done for the intention-to-treat population in both groups at 26 weeks; however, the risk of bias for these outcomes appears to be unclear, as only 88.4% and 81.4% of participants completed the study
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available and the study was not registered. One QOL measure (i.e. IPSS-QOL) has been reported, although BPHII has not been reported. The risk of bias appears to be low

Casabe 2014 (Continued)

IPSS-total, BPHII, IPSS-QOL

Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published protocol was available and the study was not registered. Adverse events have been reported, and the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published protocol was available and the study was not registered. However, the risk of bias for these outcomes appears to be low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to the placebo run-in period cannot be ruled out, as it may enrich the study population with those who were likely to be more compliant

Dmochowski 2010

Methods	Study design: randomised double-blind placebo-controlled 2-arm parallel-group study Setting: multi-centric Duration of the study: not mentioned
Participants	Inclusion criteria: men at least 40 years old with a greater than 6-month history of BPH-LUTS (with or without bladder outlet obstruction) and an IPSS-total ≥ 13 at the screening visit were eligible for enrolment unless PSA was > 10 ng/mL (men with PSA 4 to 10 ng/mL were eligible only with evidence of a prostate biopsy negative for malignancy within 12 months or stable PSA since the prior biopsy), or with PVR ≥ 350 mL at the screening visit. A 4-week washout period was required for men reporting the use of other BPH or ED therapies Exclusion criteria: men with a history of 5-ARI use within the previous 4 months; a history of penile or pelvic surgery or radiotherapy; lower urinary tract malignancy, trauma, or recent instrumentation; urinary retention or bladder stones; urethral obstruction due to stricture, valves, sclerosis, or tumour; bladder calculi; atonic, decompensated, or hypocontractile bladder; detrusor sphincter dyssynergia; intravesical obstruction; urinary tract inflammation or infection; or prostate cancer. Other exclusionary medical conditions were clinically significant renal or hepatic insufficiency; cardiovascular conditions such as significant angina, recent myocardial infarction, or poorly controlled blood pressure; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens, or a potent cytochrome P450 3A4 inhibitor or inducer; uncontrolled diabetes (glycosylated haemoglobin $> 9\%$) Total number of participants randomly assigned: 200 Age: 58.6 (9.3) years IPSS-total: 21.8 (5.6)
Interventions	Intervention (s): tadalafil 20 mg/d (n = 99) Control(s): placebo (n = 101) Washout period: 4-week washout period for those who receiving other therapies for BPH-LUTS or ED Duration of the study interventions: ≥ 12 weeks
Outcomes	Primary efficacy: uroflow pressure flow parameters (voiding pressure - PdetQmax)

Dmochowski 2010 (Continued)

Secondary efficacy: IPSS-total, IPSS-obstructive, IPSS-storage, non-invasive uroflow parameters (PVR)

Safety measures: adverse events

Notes

Source of funding has not been stated in the published manuscript. This study was registered at ClinicalTrials.gov (NCT00386009) by Eli Lilly. Employees of the company have been acknowledged in the publication. Five of 6 study authors have disclosed financial conflicts of interest with Eli Lilly, the manufacturer of tadalafil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described
Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "randomized double-blind placebo controlled study" Comment: the procedure adopted for allocation concealment is not described
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double-blind" Comment: who was masked to the interventions is not described in adequate detail
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: "double-blind" Comment: who was masked to the interventions is not described in adequate detail
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind" Comment: who was masked to the interventions is not described in adequate detail; however, these outcomes are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double-blind" Comment: whether treatment administrator or assessor was blinded is not described
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double-blind" Comment: whether treatment administrator or assessor was blinded is not described
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind" Comment: whether treatment administrator or assessor was blinded is not described; however, these outcomes are less susceptible to detection bias
Incomplete outcome data (attrition bias)	Unclear risk	Comment: IPSS-total was reported for 89/101 (88%) in tadalafil group and 82/99 (84%) in placebo group. Due to the high rate of loss of post-randomisation data, the risk of bias appears to be unclear

Dmochowski 2010 (Continued)

IPSS-total, BPHII, IPSS-QOL

Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: adverse events were reported for 101/101 participants in tadalafil group and 99/99 in placebo group; however, the risk of bias is unclear due significant loss to follow-up and treatment discontinuation
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: study authors specifically mentioned that there were no adverse events related to urinary retention in both drug (101) and placebo (99) groups. Safety reporting was done on the ITT population; therefore, the risk of bias appears to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: this study was registered at ClinicalTrials.gov (NCT00386009). Uroflowmetry and IPSS scores were reported, but no quality of life assessments were done despite the use of high doses of tadalafil. Therefore, the risk of bias appears to be unclear
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: this study was registered at ClinicalTrials.gov (NCT00386009). Assessment of adverse events was proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: this study was registered at ClinicalTrials.gov (NCT00386009). There were no adverse events related to urinary retention in both drug and placebo groups. The risk of bias appears to be low
other bias All outcomes	Low risk	Comment: no significant risk of other bias

Egerdie 2012

Methods	Study design: randomised double-blind placebo-controlled 3-arm parallel-group study Setting: multi-centric Duration of the study: not mentioned
Participants	Inclusion criteria: sexually active men ≥ 45 years of age who had a 3-month history of ED and BPH-LUTS for longer than 6 months, as clinically diagnosed by a qualified physician, were eligible for screening. Histological confirmation of BPH was not required. Men reporting the use of other treatments for ED, BPH, or overactive bladder were required to complete a 4-week washout period before entering the placebo lead-in period; those not requiring washout could enter the placebo lead-in period after screening results were assessed. To continue into the placebo lead-in period, a IPSS-total score of 13 and a maximum urinary flow rate (Qmax) of 4 to 15 mL/s obtained from a valid uroflowmetry assessment were required; after the placebo lead-in period, requalification based on these criteria was not required. During the placebo lead-in period, men had to make 4 intercourse attempts with an adult female partner (as recorded in the Sexual Encounter Profile diary (SEP)) and had to be at least 70% compliant with dosing to be eligible for randomisation Exclusion criteria: history of ED caused by other primary sexual disorders, by untreated endocrine disease, or by prior non-responsiveness to PDE ₅ inhibitor therapy; certain cardiac conditions such as conduction defects, uncontrolled supraventricular arrhythmias, ventricular tachycardias, history of resuscitated cardiac arrest, or evidence of heart disease Class II per New York Heart Association classification; a prostate-specific antigen > 10 ng/mL (or 4 to 10 ng/mL, if malignancy had not been ruled out); a

Egerdie 2012 (Continued)

postvoid residual volume (PVR) 300 mL; use of finasteride or dutasteride within 3 or 6 months, respectively; lower urinary tract instrumentation within 30 days; history of urethral or intravesical obstruction; urinary retention or lower urinary tract stones within 6 months; and neurogenic bladder, renal insufficiency, or hepatic impairment

Total number of participants randomly assigned: 606

Age: 62.5 (45.3 to 83.2) years

IPSS-total: 18.3 (5.6)

Interventions	<p>Intervention(s): tadalafil 2.5 mg/d (n = 198), tadalafil 5 mg/d (n = 208)</p> <p>Control(s): placebo (n = 200)</p> <p>Run-in period: 4-week washout period followed by 4-week placebo run-in period</p> <p>Duration of the study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: IPSS-total, IIEF-EF domain</p> <p>Key secondary efficacy: sexual encounter profile question no. 3 (SEP-Q3), BPH Impact Index (BPHII)</p> <p>Additional secondary efficacy: IIEF intercourse and overall satisfaction domains, IIEF Q3 (penetration), IIEF Q4 (maintenance of erection), SEP Q2 (insertion), SEP Q4 (hardness), and SEP Q5 (overall satisfaction); those assessing BPH symptoms included the IPSS storage and voiding subscores, IPSS nocturia question, and IPSS-Quality of Life (QOL) Index. Overall assessment questionnaires included the EF general assessment question (GAQ) (whether treatment improved erections and ability to engage in sexual activity) for ED and the Patient and Clinical Global Impression of Improvement instruments (PGI-I and CGI-I, respectively)</p> <p>Safety assessments: TEAEs, SAEs, orthostatic vital signs (blood pressure and heart rate), and clinical laboratory, uroflowmetry, and PVR assessments</p>
Notes	<p>This study was sponsored by Eli Lilly and Company. Five of 8 study authors disclosed receiving funds from the sponsor; 2 were employees of the sponsor and 1 had a contract with the sponsor</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Low risk	<p>Quote: "computer generated random sequence"</p> <p>Comment: method used for random sequence generation seems to be adequate</p>
Allocation concealment (selection bias) All outcomes	Low risk	<p>Quote: interactive voice response system for treatment allocation</p> <p>Comment: method used for allocation concealment seems to be adequate</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	<p>Quote: "double blind - subject, study site personnel, and sponsor were blinded"</p> <p>Comment: who was blinded is described in adequate detail</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	<p>Quote: "double blind - subject, study site personnel, and sponsor were blinded"</p> <p>Comment: who was blinded is described in adequate detail</p>

Egerdie 2012 (Continued)

Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind - subject, study site personnel, and sponsor were blinded" Comment: who was blinded is described in adequate detail; nevertheless, these outcomes are objective in nature and are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double blind - subject, study site personnel, and sponsor were blinded" Comment: who was blinded is described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Low risk	Quote: "double blind - subject, study site personnel, and sponsor were blinded" Comment: who was blinded was described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind - subject, study site personnel, and sponsor were blinded" Comment: who was blinded is described in adequate detail; nevertheless, these outcomes are objective in nature and are less susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: for these outcomes, 184/208 (88.5%) in tadalafil 5 mg group, 172/198 (86.9%) in tadalafil 2.5 mg group, and 170/200 (85%) in placebo group completed the study; however, IPSS-total and BPHII have been reported for 208/208, 198/198, and 200/200 participants. Risk of bias is unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 184/208 (88.5%) in tadalafil 5 mg group; 172/198 (86.9%) in tadalafil 2.5 mg group, and 170/200 (85%) in placebo group completed the study; however, adverse effects were reported for 208/208, 198/198, and 200/200 participants. Risk of bias is unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 184/208 (88.5%) in tadalafil 5 mg group, 172/198 (86.9%) in tadalafil 2.5 mg group, and 170/200 (85%) in placebo group completed the study. Although the reported incidence for these outcomes is none, the risk of bias is unclear
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: published protocol or study registration could not be traced. Relevant outcomes have been reported, and the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: published protocol or study registration could not be traced. Adverse events have been reported for all included participants, and the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: published protocol or study registration could not be traced. The reported incidence for these outcomes is none. The risk of bias appears to be low

Egerdie 2012 (Continued)

other bias All outcomes	Unclear risk	Comment: potential bias due to the placebo run-in period cannot be ruled out. as it may select for compliant participants
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Gacci 2012

Methods	Study design: randomised double-blind placebo-controlled 2-arm parallel-group study Setting: single centre Duration of the study: not mentioned
Participants	Inclusion criteria: age 40 to 80 years, LUTS (defined as IPSS-12, Overactive Bladder Questionnaire, Short Form) (OAB-q SF) 8), voided volume < 400 mL (as verified by bladder diary, with the aim to include men with normal bladder capacity), maximum flow rate > 5 mL/s (with voided volume > 150 mL), signed informed consent Exclusion criteria: hypersensitivity to vardenafil or tamsulosin, drugs with proven or suspected incompatibility with vardenafil or tamsulosin bladder failure (proven by abnormal urodynamic assessment, performed in men with post-void residual (PVR) urine volume > 250 mL) or neurogenic bladder (multiple sclerosis, Parkinson's, and spinal cord injury), urinary tract infection, LUT disease/treatment (urethral stenosis, 5-ARI, and BPH surgery), severe systemic disease (hepatic, cardiac, haematological disease, and neoplasm), and unable to complete the protocol. ED or any previous treatment for ED was not considered an exclusion criterion Total number of participants randomly assigned: 60 Age: 67.9 (7.5) years IPSS-total: 19.5 (0.9)
Interventions	Intervention(s): tamsulosin 0.4 mg/d + vardenafil 10 mg/d (n = 30) Control(s): tamsulosin 0.4 mg/d (n = 30) Run-in period: 4-week drug-free washout period followed by 2-week active drug (tamsulosin 0.4 mg/d) period Duration of the study intervention: 12 weeks
Outcomes	Primary efficacy: IPSS-total, IPSS-storage, IPSS-voiding, IPSS-bother score, OAB-q SF, International Index of Erectile Function, version 5 (IIEF-5) Secondary efficacy: maximum flow rate (Qmax), average flow rate (Qave), voided volume (Vcomp), PVR volume Safety assessments: adverse events, laboratory parameters, electrocardiogram abnormalities
Notes	There is no statement on sponsorship, and study authors declared conflicts of interest as none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Low risk	Quote: "computer-generated pseudo-random code, using the method of random permuted blocks. An exclusive randomization number was assigned to each patient" Comment: method used for random sequence generation appears to be adequate

Gacci 2012 (Continued)

Allocation concealment (selection bias) All outcomes	Unclear risk	Comment: method used for allocation concealment is not described in the published manuscript.
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate and risk of bias for these outcomes appears to be low
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate and risk of bias for this outcome appears to be low
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate and to further these outcomes, as they are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate and the risk of bias appears to be low for these outcomes
Blinding of outcome assessment (detection bias) AE and treatment related harms	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate and the risk of bias appears to be low for this outcome
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; "in order to assure double-blind procedure, placebo and vardenafil were prepared as identical capsules" Comment: appears to be adequate; further these outcomes are less susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 30/30 (100%) in tamsulosin + vardenafil group and 29/30 (99%) in tamsulosin + placebo group completed the 12-week study. The risk of bias appears to be low for this outcome assessment
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 30/30 (100%) in tamsulosin + vardenafil group and 29/30 (99%) in tamsulosin + placebo group completed the 12-week study. The risk of bias appears to be low for this outcome assessment
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the risk of bias appears to be low for this outcome assessment. The reported incidence for these outcomes is none. Moreover, these outcomes are less susceptible to attrition bias
Selective reporting (reporting bias)	Unclear risk	Comment: no published protocol was available and the study registration could not be traced. The QOL parameters have not been reported, which was

Gacci 2012 (Continued)

IPSS-total, BPHII, IPSS-QOL		relevant for combination therapy. Therefore, the risk of bias appears to be unclear
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published protocol was available and study registration could not be traced. Adverse events have been reported, and the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published protocol was available and the study registration could not be traced. The reported incidence of these outcomes is none, and the risk of bias is low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to active drug run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant and/or less likely to experience adverse events

Kim 2011

Methods	Study design: double-blind placebo- and active drug-controlled 3-arm parallel-group study Setting: multi-centric Duration of the study: not mentioned
Participants	Inclusion criteria: men 45 years of age and older with BPH and history of LUTS longer than 6 months at visit 1, bladder outlet obstruction of intermediate severity ($Q_{max} \geq 4$ to ≤ 15 mL/s), and IPSS-total ≥ 13 after the run-in period were eligible for randomisation Exclusion criteria: PSA > 10 ng/mL, postvoid residual volume (PVR) > 300 mL, history of symptomatic orthostatic hypotension, dizziness, vertigo, loss of consciousness or syncope, PSA values from 4 to 10 ng/mL, negative prostate biopsy for malignancy within 12 months, used finasteride within 3 months or dutasteride within 6 months Total number of participants randomly assigned: 151 Age: 61.6 (6.6) years IPSS-total: 17.4 (5.1)
Interventions	Intervention(s): tadalafil 5 mg/d (n = 51), tamsulosin 0.2 mg/d (n = 49) Control(s): placebo (n = 51) Run-in period: 4-week drug-free washout period followed by 2-week placebo run-in period Duration of study interventions: 12 weeks
Outcomes	Primary efficacy: IPSS-total at 12 weeks for tadalafil 5 mg vs placebo Secondary efficacy: IPSS obstructive and irritative subscores, IPSS nocturia question, IPSS-QOL Index, BPH Impact Index (BPHII), Patient Global Impression of Improvement (PGI-I), Clinician Global Impression of Improvement (CGI-I), uroflowmetry, safety measures, comparison of tamsulosin vs placebo for all assessments Safety assessments: adverse events, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PVR, urinalysis for 12 weeks

Kim 2011 (Continued)

Notes

The source of funding for the study is not stated in the manuscript. This study was registered by Eli Lilly and Company at Clinicaltrials.gov. Ten of 14 study authors have not disclosed any conflicts of interest. Remaining 4 study authors (including the corresponding author) were employees or shareholders or advisors of Eli Lilly and Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described in adequate detail
Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "randomly assigned (1:1:1) ratio to receive..." Method of allocation concealment is not mentioned Comment: the procedure adopted for allocation concealment is not described in adequate detail
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double-blind" Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: "double-blind" Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind" Comment: probably done, but who was blinded is not described in adequate detail; however, the risk of bias appears to be low, as these outcomes are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double-blind" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double-blind" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail; however, these outcomes are less susceptible to detection bias
Incomplete outcome data (attrition bias)	Low risk	Comment: 48/51 (95%) in tadalafil group, 48/49 (94%) in tamsulosin group, and 47/51 (93%) in placebo group completed the study of 12 weeks. These out-

Kim 2011 (Continued)

IPSS-total, BPHII, IPSS-QOL		comes have been reported for 49, 51, and 51 participants, respectively. The risk of bias appears to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 48/51 (95%) in tadalafil group, 48/49 (94%) in tamsulosin group, and 47/51 (93%) in placebo group completed the study of 12 weeks. Adverse events have been reported for 49, 51, and 51 participants respectively. The risk of bias appears to be low
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: 48/51 (95%) in tadalafil group, 48/49 (94%) in tamsulosin group, and 47/51 (93%) in placebo group completed the study of 12 weeks. The reported incidence for these outcomes is none. The risk of bias appears to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the clinical trial was registered at ClinicalTrials.gov as NCT00540124. These outcomes were proposed and reported. The risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: the clinical trial was registered at ClinicalTrials.gov as NCT00540124. Adverse events were proposed and reported. The risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the clinical trial was registered at ClinicalTrials.gov as NCT00540124. These outcomes were proposed and reported. The reported incidence for these outcomes is none. The risk of bias appears to be low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant and/or likely to experience fewer adverse events

McVary 2007a

Methods	Study design: randomised double-blind placebo-controlled 2-arm parallel-group study Setting: multi-centric Duration of the study: 29 March 2004 to 20 May 2005
Participants	Inclusion criteria: men 45 years of age or older with a clinical diagnosis of ED (score ≤ 25 on the EF domain of the IIEF) and IPSS-total score ≥ 12 Exclusion criteria: confirmed or suspected prostate malignancy, serum prostate-specific antigen > 10 ng/mL, previous invasive intervention for BPH, previous prostate or bladder/pelvic radiation or surgery. Participants who had prostate specific antigen 10 ng/ml or less and 4 ng/ml or greater required 2 additional forms of documentation, such as digital rectal examination, negative biopsy (must not have been performed within 8 weeks of the study) or negative transrectal ultrasound performed within 6 months of the study, to show that the patient was clinically free of malignancy. Participants with active urinary tract disease, underwent cystoscopy within 4 weeks of the study, calculi in the urinary tract or acute urinary retention within 6 months of the study, recurrent urinary tract infection or catheterisation for outflow obstruction in the year before the study, other known or suspected causes of urinary symptoms other than BPH, hypotension ($< 90/50$ mmHg), hypertension ($> 170/110$ mmHg), orthostatic hypotension, significant cardiovascular disease. Use of nitrates in any form was prohibited. Patients with hepatic or renal dysfunction (hepatic enzymes > 1.5 times the upper

McVary 2007a (Continued)

limit of normal and/or serum creatinine > 150 mol/L), poorly controlled diabetes (HbA1C > 7%), history of retinitis pigmentosa. Use of antimuscarinics was prohibited, as was use of 5-ARI within 6 months or at any time during the study and alpha-blockers within 4 weeks or at any time during the study

Total number of participants randomly assigned: 370

Mean Age: 60 (SD=8.6) years

IPSS-total: values at baseline not reported

Interventions	<p>Intervention(s): sildenafil 50 mg to 100 mg daily (n = 189)</p> <p>Control(s): placebo (n = 180)</p> <p>Run-in period: none</p> <p>Duration of study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: change from baseline in EF assessed using the EF domain of the IIEF</p> <p>Secondary efficacy: changes from baseline in the other domains of the IIEF, LUTS using the I-PSS, I-PSS QOL question, BPHII, Qmax, SEAR scores, end of treatment satisfaction using EDITS</p> <p>Safety measures: all observed or volunteered AE were recorded for the study duration and for 1 week after the last dose of study medication</p>
Notes	<p>Funding source and conflicts of interest were not stated in the manuscript</p> <p>How many participants needed dose titration and the median dose received by participants were not reported</p> <p>Efficacy data for 50 mg and 100 mg sildenafil vs placebo were not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Low risk	<p>Quote: "computer generated pseudo-random code in a 1:1 ratio by study centre with fixed block size of 4"</p> <p>Comment: the method used for random sequence generation appears to be adequate</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "participants were randomly assigned blinded medications"</p> <p>Comment: the procedure adopted for allocation concealment was not described in adequate detail</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	<p>Quote: "double blind"</p> <p>Comment: probably done, but who was blinded is not described in adequate detail</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	<p>Quote: "double blind"</p> <p>Comment: probably done, but who was blinded is not described in adequate detail</p>

McVary 2007a (Continued)

Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, as they are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" Comment: probably done, but whether outcome assessors were blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: probably done, but whether outcome assessors were blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: probably done, but whether outcome assessors were blinded was not described in adequate detail. The risk of bias appears to be low for these outcomes, as they are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 168/187 (89%) participants in tadalafil group and 155/179 (86%) participants in placebo group completed the 12-week study period. IPSS-total was reported for 162/179 and 179/187; BPHII for 170/187 and 181/189; and IPSS-QOL for 170/187 and 181/189 participants. Due to this discrepancy, the risk of bias appears to be unclear
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 168/187 (89%) participants in tadalafil group and 155/179 (86%) participants in placebo group completed the 12-week study period. Although adverse events were reported for 180/187 and 189/189 participants in placebo and sildenafil groups, the risk of bias appears to be unclear due to considerable attrition
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 168/187 (89%) participants in tadalafil group and 155/179 (86%) participants in placebo group completed the 12-week study period. The reported incidence for these outcomes is none. Risk of bias appears to be unclear due to considerable attrition
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the sponsor registered the study at ClinicalTrials.gov (NCT00143221). All relevant outcomes were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: the sponsor registered the study at ClinicalTrials.gov (NCT00143221). Adverse event assessments were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the sponsor registered the study at ClinicalTrials.gov (NCT00143221). The reported incidence for these outcomes is none. However, these outcomes are less susceptible to risk of bias
other bias All outcomes	Unclear risk	Comment: potential risk of bias in efficacy assessment due to improper reporting of study results. Study authors mentioned that participants receiving 50

McVary 2007a (Continued)

mg sildenafil were excluded if they had an adverse event or showed signs that treatment may be ineffective. This may compromise the external validity

McVary 2007b

Methods	<p>Study design: randomised double-blind placebo-controlled 2-arm parallel-group study</p> <p>Setting: multi-centric</p> <p>Duration of the study: November 2004 to July 2005</p>
Participants	<p>Inclusion criteria: men 45 years of age or older with a history of LUTS secondary to BPH lasting 6 months or longer were eligible for this study. Patients agreed not to use other BPH medications during the study</p> <p>Exclusion criteria: PSA > 10 ng/mL (for men with PSA 4 to 10 ng/mL, a recent prostate biopsy negative for malignancy was required); recent finasteride (prior 3 months) or dutasteride (prior 12 months) treatment; history of radical prostatectomy or other pelvic surgery; neurological condition affecting bladder function; recent lower urinary tract instrumentation, urinary retention, or bladder stones; history of urethral obstruction due to stricture, valves, sclerosis, or tumour; detrusor sphincter dyssynergia; urinary tract inflammation or infection; intravesical obstruction secondary to prostate median lobe; prostate cancer; PVR ≥ 200 mL at visit 2; certain cardiovascular diseases, for example, unstable angina, recent myocardial infarction, or poorly controlled blood pressure; clinically significant renal or hepatic insufficiency; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens, or a potent cytochrome P450 3A4 inhibitor; uncontrolled diabetes (glycosylated HbA > 9%)</p> <p>Total number of participants randomly assigned: 281</p> <p>Mean Age: 61.3 (range 45 to 82.3) years</p> <p>Mean IPSS-total: 17.9 (SD values at baseline not reported)</p>
Interventions	<p>Intervention(s): tadalafil 5 mg to 20 mg/d (n = 138), tadalafil 5 mg to 20 mg/d (n = 138)</p> <p>Control(s): placebo (n = 143)</p> <p>Run-in period: 4-week drug-free washout period followed by 4 weeks of single-blind placebo run-in preceding the double-blind study period</p> <p>Duration of study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: I-PSS change from baseline (visit 3) to 6 and 12 weeks</p> <p>Secondary efficacy: change from baseline to 6 and 12 weeks in I-PSS irritative domain (questions 2, 4, and 7); I-PSS obstructive domain (questions 1, 3, 5, and 6); IPSS QOL Index; BII; LUTS GAQ; Qmax; Qave; Vcomp. Post hoc analyses were done to examine changes at 6 and 12 weeks vs visit 2, before the placebo run-in. In sexually active patients, EF was assessed using the IIEF EF domain (questions 1 to 5 and 15). Scores are presented for the participant subset that was sexually active and had ED, with ED assessed by the investigator at visit 1. Post hoc analyses were done to examine I-PSS in this participant subset</p> <p>Safety measures: safety was assessed by monitoring the incidence of patient-reported adverse events and changes in clinical laboratory values (including PSA), PVR, and vital signs</p>
Notes	<p>This study was supported by Lilly ICOS LLC, and 8/8 study authors have declared financial interests and/or relationships with the company</p> <p>The dose of tadalafil was increased from 5 mg/d to 20 mg/d after 6 weeks. Study authors did not report whether all participants tolerated such high doses of the drug or if some of them needed de-escalation</p>

McVary 2007b (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomly assigned in geographic regions" Comment: the process of random sequence generation was not described in adequate detail
Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "randomly assigned in geographic regions to 6 weeks treatment of once daily Tadalafil 5mg followed by 6 weeks escalation to 20mg/d or placebo in 1:1 ratio" Comment: the procedure adopted for allocation concealment is not described in adequate detail
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, as they are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind" Comment: probably done, but whether outcome assessors were blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: probably done, but whether outcome assessors were blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind" Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, as they are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 129/138 (93%) in tadalafil group and 133/143 (93%) in placebo group completed the 12-week study period. IPSS-total, BPHII, and IPSS-QOL were reported for 143/143 and 138/138 participants. The risk of bias appears to be low due to attrition
Incomplete outcome data (attrition bias)	Low risk	Comment: 129/138 (93%) in tadalafil group and 133/143 (93%) in placebo group completed the 12-week study period, and safety outcomes have been

McVary 2007b (Continued)

AE and treatment related harms		reported for 138 and 143 participants, respectively. The risk of bias appears to be low due to attrition
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comments: 129/138 (93%) in tadalafil group and 133/143 (93%) in placebo group completed the 12-week study period, and safety outcomes have been reported for 138 and 143 participants, respectively. The reported incidence of these outcomes is none, and the risk of bias appears to be low due to attrition
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: no published protocol was available and study registration could not be traced. Relevant outcomes have been reported and the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published protocol was available and study registration could not be traced. However, adverse events have been reported and the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published protocol was available and study registration could not be traced. Reported incidences for these outcomes is none. However, the risk of bias appears to be low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant

Oelke 2012

Methods	Study design: randomised double-blind placebo-controlled 3-arm parallel-group 12-week study Setting: multi-centric Duration of the study: December 2009 to January 2011
Participants	Inclusion criteria: men 45 years of age who had LUTS/BPH for longer than 6 months at screening and with IPSS 13 and maximum urinary flow rate (Qmax) 4 to 15 mL/s before placebo lead-in period; patients with improvement in IPSS or Qmax during placebo lead-in were not excluded. Compliance 70% during placebo lead-in was required for randomisation. Men should not have used finasteride or dutasteride within 3 or 6 months, respectively Exclusion criteria: tamsulosin-specific exclusions of men with planned cataract surgery; history of symptomatic orthostatic hypotension (especially upon initial alpha-blocker administration); recurrent dizziness, vertigo, loss of consciousness, or syncope Total number of participants randomly assigned: 511 Mean Age: 63.6 (range 45.1 to 88.6) Mean IPSS-total: 17.1 (SD = 5.4)
Interventions	Intervention(s): tamsulosin 0.4 mg/d (n = 168); tadalafil 5 mg/d (n = 171) Control(s): placebo (n = 172) Run-in period: 4-week washout period, followed by 4-week placebo lead-in period before randomisation

Oelke 2012 (Continued)

Duration of study interventions: 12 weeks

Outcomes	<p>Primary efficacy: IPSS-total</p> <p>Secondary efficacy: BPHII; IIEF-EF; week 1 IPSS (mIPSS) using questions beginning with "Since your last visit"; IPSS storage and voiding subscores; nocturia question (question 7); IPSS Quality-of-Life (QOL) Index; Patient and Clinician Global Impression of Improvement (PGI-I and CGI-I, respectively); patient-rated Treatment Satisfaction Scale-BPH (TSS-BPH)</p> <p>Safety measures: patient-reported adverse events, PVR, clinical laboratory parameters (haematology, chemistry, and urinalysis), vital signs. TEAE were those first reported or worsening after randomisation</p>
Notes	<p>Funding support and role of the sponsor: Eli Lilly and Company helped design and conduct and provided support for this study. Data collection and management and all statistical analyses were performed and retained by the sponsor. The lead author has disclosed financial benefits from the sponsor, and the other 5 study authors were consultants or employees of the sponsor</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	<p>Quote: "randomization was stratified....."</p> <p>Comment: the process of random sequence generation was not described in adequate detail</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "randomization was stratified....."</p> <p>Comment: the procedure adopted for allocation concealment was not described in adequate detail</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	<p>Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	<p>Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	<p>Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Low risk	<p>Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)"</p> <p>Comment: the risk of bias appears to be low</p>
Blinding of outcome assessment (detection bias) AE and treatment related harms	Low risk	<p>Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)"</p>

Oelke 2012 (Continued)

		Comment: the risk of bias appears to be low
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: the manuscript mentions, "Double blind"; the published protocol (NCT00970632) mentions "Masking: Double Blind (Subject, Investigator, Outcomes Assessor)" Comment: the risk of bias appears to be low
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 156/171 (91%) in tadalafil group, 150/168 (89.3%) in tamsulosin group, and 148/172 (86%) in placebo group completed the 12-week study period IPSS-total: reported for 171/171, 165/167, and 172/172 BPHII: the numbers are not mentioned IPSS-QOL: reported for 171/171, 165/167, and 172/172 participants The risk of bias due to attrition appears to be unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 156/171 (91%) in tadalafil group, 150/168 (89.3%) in tamsulosin group, and 148/172 (86%) in placebo group completed the 12-week study period. Adverse events have been reported for 171, 168, and 171 participants. The risk of bias due to attrition appears to be unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 156/171 (91%) in tadalafil group, 150/168 (89.3%) in tamsulosin group, and 148/172 (86%) in placebo group completed the 12-week study period. Study authors have reported no events for these outcomes; however, the risk of bias due to attrition appears to be unclear
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00970632). Outcomes have been reported, and the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00970632). The risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00970632). The risk of bias appears to be low
other bias All outcomes	Unclear risk	Comment: Potential risk of bias due to placebo run-in period cannot be ruled out, as it may enrich the study population with those who were more compliant

Porst 2011

Methods	Study design: double-blind placebo-controlled 2-arm parallel-design study Setting: multi-centric
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Porst 2011 (Continued)

Duration of the study: not specified

Participants	<p>Inclusion criteria: men 45 years of age with BPH-LUTS for longer than 6 months at screening were eligible. A digital rectal examination was performed at screening; an ultrasound assessment of prostate volume was not performed, and histological verification of prostatic hyperplasia was not required. Patients reporting use of BPH, overactive bladder, or ED therapy underwent a 4-week treatment-free washout period; otherwise, a 4-week single-blind placebo lead-in period began after screening. Inclusion criteria before the placebo lead-in period included total IPSS of 13 and Qmax 4 to 15 mL/s obtained from a uroflowmetry assessment meeting prespecified criteria. During the placebo lead-in period, patients had to be 70% compliant with dosing to qualify for randomisation; those whose IPSS or Qmax improved were not excluded</p> <p>Exclusion criteria: PSA > 10.0 ng/mL (if 4.0 to 10.0 ng/mL, malignancy had to be ruled out) or postvoid residual (PVR) volume 300 mL at screening; finasteride or dutasteride use within 3 or 6 months, respectively, of visit 2; lower urinary tract instrumentation within 30 days; urinary retention or lower urinary tract stones within 6 months; history of urethral and/or proven bladder neck obstruction; neurogenic bladder; creatinine clearance < 30 mL/min; severe hepatic impairment; certain cardiovascular conditions; current nitrate therapy</p> <p>Total number of participants randomly assigned: 375</p> <p>Mean Age: 65.8 (SD = 9.1) years</p> <p>IPSS-total: baseline values are not mentioned</p>
Interventions	<p>Intervention: tadalafil 5 mg/d (n = 161)</p> <p>Control(s): placebo (n = 164)</p> <p>Run-in period: 4-week washout period, followed by 4-week placebo run-in period</p> <p>Duration of study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: IPSS-total</p> <p>Secondary efficacy: IIEF-EF; BPHII; IPSS questions modified (mIPSS) to begin with "Since your last visit" rather than "Over the past month" for the week 1 assessment. IPSS-storage and voiding subscores, nocturia question, and IPSS-QOL; Patient and Clinician Global Impression of Improvement (PGI-I and CGI-I, respectively)</p> <p>Safety measures: patient-reported AE, orthostatic vital signs, PVR, and uroflowmetry and clinical laboratory parameters. A TEAE was defined as an AE that was first reported or worsened after randomisation. A positive orthostatic test met 1 of the following criteria (assessed from supine to standing position): systolic blood pressure decrease of 20 mmHg, diastolic blood pressure decrease of 10 mmHg, heart rate increase of 20 beats per minute, unable to remain standing. A treatment-emergent positive orthostatic test was a positive test at any post-baseline visit among patients with a normal baseline test</p>
Notes	<p>Funding/support and role of the sponsor: Eli Lilly and Company helped design and conduct and provided support for this study. Data collection and all statistical analyses were performed and retained by the sponsor. Four of 8 study authors declared financial conflicts of interest with the sponsor for being investigators/speakers/consultants; 4 of the other study authors were employees and stockholders of the sponsor</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described

Porst 2011 (Continued)

Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "randomized, double-blind, placebo-controlled" Comment: the procedure adopted for allocation concealment is not described
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double blind"; the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done; the risk of bias appears to be low
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	Quote: "double blind"; the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done; the risk of bias appears to be low
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind"; the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done; the risk of bias appears to be low for these outcomes, as they are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind"; the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double blind", the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: Probably done, but it was not described in adequate detail, whether the treatment administrator or assessor was blinded
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind"; the published protocol (NCT00827242) mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, as they are less susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 152/164 (91.9%) in tadalafil group and 152/164 (92.7%) in placebo group completed the 12-week study period. For analyses of these outcomes for change from baseline to week 12, LOCF was imputation was applied. These outcomes were reported for 164 and 161 participants. The risk of bias due to attrition was judged to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 152/164 (91.9%) in tadalafil group and 152/164 (92.7%) in placebo group completed the 12-week study period. Adverse events were reported for all participants. The risk of bias due to attrition was judged to be low
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: 152/164 (91.9%) in tadalafil group and 152/164 (92.7%) in placebo group completed the 12-week study period. The risk of bias due to attrition was judged to be low, as the risk of these events is low

Porst 2011 (Continued)

Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00827242). These outcomes were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00827242). These outcomes were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00827242). These outcomes were proposed and reported. Reported incidence for these outcomes is none; however, these outcomes are objective and the risk of bias was judged to be low
other bias All outcomes	Low risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant

Regadas 2013

Methods	Study design: randomised double-blind placebo-controlled 2-arm parallel-group study Setting: single centre Duration of the study: October 2010 to September 2011
Participants	Inclusion criteria: men who are at least 45 years old complaining of BPH/LUTS, evaluated with pressure flow study (PFS) and IPSS. Only patients with Bladder Outlet Obstruction Index (BOOI) > 20 and IPSS score > 14 Exclusion criteria: suspect or confirmed prostate cancer; LUTS not related to BPH; hypotension; retinitis pigmentosa; use of 5a-reductase inhibitor in the last 6 months; use of a-blockers, anticholinergics, or PDE inhibitors in the last month; surgery of the prostate, urethra, or bladder; presence of neurological disease; urinary retention; bladder stones; use of nitrates; cardiovascular, hepatic, or renal insufficiency Total number of participants randomly assigned: 40 Mean Age: 60.4 (SD = 1.8) years Mean IPSS-total: 20.5 (SD = 4.1)
Interventions	Intervention(s): tadalafil 5 mg/d + tamsulosin 0.4 mg/d (n = 20) Control(s): tamsulosin 0.4 mg/d + placebo (n = 20) Run-in period: none Duration of study interventions: 30 days
Outcomes	Primary efficacy: changes in urodynamic variables of the voiding phase - PdetQmax, Qmax - from baseline to week 4 Secondary efficacy: IPSS-total, IPSS-voiding, IPSS-storage Safety measures: adverse events

Regadas 2013 (Continued)

Notes The source of funding and conflicts of interest were not stated in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described
Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "double-blind...." Comment: the procedure adopted for allocation concealment is not described
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind..." Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: "double blind...." Comment: probably done, but who was blinded is not described in adequate detail
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind...." Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, which are not susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double blind...." Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double blind" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double blind...." Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, which are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 20/20 (100%) participants in tadalafil + tamsulosin group and 20/20 (100%) participants in tamsulosin + placebo group completed the 4-week study period, and IPSS-total has been reported for all. The risk of bias due to attrition appears to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 20/20 (100%) participants in tadalafil + tamsulosin group and 20/20 (100%) participants in tamsulosin + placebo group completed the 4-week study period and 1 adverse event has been reported. The risk of bias due to attrition was judged to be low

Regadas 2013 (Continued)

Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: 20/20 (100%) participants in tadalafil + tamsulosin group and 20/20 (100%) participants in tamsulosin + placebo group completed the 4-week study period. No incidence of acute urinary retention or need for surgical intervention reported. The risk of bias due to attrition was judged to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: no published study protocol available and study registration could not be traced. No quality of life assessments have been reported for participants. The risk of bias appears to be unclear
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published study protocol available and study registration could not be traced. 1 adverse event has been reported for the combination treatment group. The risk of bias appears to be low for these outcomes
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published study protocol available and study registration could not be traced. The reported incidence for these outcomes is none. The risk of bias appears to be low
other bias All outcomes	Low risk	Comment: Study had no significant risk of other bias

Roehrborn 2008

Methods	Study design: randomised double-blind placebo-controlled 5-arm dose-finding parallel-group study Setting: multi-centric Duration of the study: not mentioned
Participants	Inclusion criteria: men at least 45 years old with a history of LUTS secondary to BPH of 6 months or longer, IPSS-total ≥ 13 , Qmax 4 to 15 mL per second from pre-void bladder volume, as assessed by ultrasound, and between 150 and 550 mL with voided volume of 125 mL Exclusion criteria: PSA > 10 ng/mL (in men with PSA 4 to 10 ng/mL, prostate biopsy negative for malignancy within 12 months was required) or PVR volume ≥ 300 mL; recent finasteride or dutasteride treatment within 3 and 12 months, respectively, before visit 2 (the start of the placebo run-in period); penile or pelvic surgery; radiotherapy; lower urinary tract malignancy; trauma or recent instrumentation; urinary retention or bladder stones; history of urethral obstruction due to stricture, valves, sclerosis, or tumour; neurological condition affecting bladder function; detrusor-sphincter dyssynergia; intravesical obstruction secondary to prostate median lobe; urinary tract inflammation or infection; prostate cancer. Other exclusionary medical conditions were clinically significant renal or hepatic insufficiency; cardiovascular conditions such as significant angina, recent myocardial infarction, or poorly controlled blood pressure; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens, or a potent cytochrome P450 3A4 inhibitor; uncontrolled diabetes (glycosylated HbA1c > 9%) Total number of participants randomly assigned: 1058 Mean Age: 62.1 (range 44.99 to 92.64) years Mean IPSS-total: 17.4 (SD = 5.8)
Interventions	Intervention(s): tadalafil 2.5 mg/d (n = 208); tadalafil 5 mg/d (n = 212); tadalafil 10 mg/d (n = 216); tadalafil 20 mg/d (n = 209)

Roehrborn 2008 (Continued)

Control(s): placebo (n = 211)

Run-in period: 4-week washout period for those who were previously treated and/or 4-week placebo run-in period

Duration of study interventions: 12 weeks

Outcomes	<p>Primary efficacy: change in IPSS-total after 12 weeks with 5 mg/d</p> <p>Secondary efficacy: change in IPSS-total after 12 weeks with 2.5 mg/d, 10 mg/d, or 20 mg/d compared to placebo; dose-response evaluation; IPSS-subscores; BPHII; GAQ; Qmax; IIEF</p> <p>Safety measures: patient-reported TEAEs, SAEs, vital signs, changes in clinical laboratory values, including PSA and PVR</p>
Notes	Study was supported by Eli Lilly and Company (CR, KTM). Study authors provided no statement on conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized"</p> <p>Comment: the process of random sequence generation is not described</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized, double-blind"</p> <p>Comment: the procedure adopted for allocation concealment is not described. Therefore, the risk of bias is unclear for all outcome assessments</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	<p>Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)"</p> <p>Comment: probably done, and the risk of bias was judged to be low</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	<p>Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)"</p> <p>Comment: probably done, and the risk of bias was judged to be low</p>
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	<p>Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)"</p> <p>Comment: probably done, and the risk of bias appears to be low, as these outcomes are objective and are not susceptible to performance bias</p>
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	<p>Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)"</p> <p>Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail</p>
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	<p>Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)"</p>

Roehrborn 2008 (Continued)

		Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; the registered study NCT00384930 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail. The risk of bias appears to be low for these outcomes, which are less susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 185/212 (87.3%) in placebo group, 182/209 (87.1%) in tadalafil 2.5 mg/d group, 182/212 (85.9%) in tadalafil 5 mg/d group, 175/216 (81%) in tadalafil 10 mg/d group, and 162/209 (77.5%) in tadalafil 20 mg/d group completed the 12-week study period. Study authors have reported IPSS-total and IPSS-QOL for 212, 208, 212, 216, and 208 participants. The risk of bias due to attrition is unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 185/212 (87.3%) in placebo group, 182/209 (87.1%) in tadalafil 2.5 mg/d group, 182/212 (85.9%) in tadalafil 5 mg/d group, 175/216 (81%) in tadalafil 10 mg/d group, and 162/209 (77.5%) in tadalafil 20 mg/d group completed the 12-week study period. Adverse events were reported for all participants. The risk of bias due to attrition is unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 185/212 (87.3%) in placebo group, 182/209 (87.1%) in tadalafil 2.5 mg/d group, 182/212 (85.9%) in tadalafil 5 mg/d group, 175/216 (81%) in tadalafil 10 mg/d group, and 162/209 (77.5%) in tadalafil 20 mg/d group completed the 12-week study period. The risk of bias due to attrition is unclear due to considerable loss of post-randomisation data
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00384930). These outcomes were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00384930). These outcomes were proposed and reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the study was registered by the sponsor at ClinicalTrials.gov (NCT00384930). The reported incidence for these outcomes is none. However, the risk of bias is low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who are more compliant

Stief 2008

Methods	Study design: randomised double-blind placebo-controlled 12-week study Setting: multi-centric Duration of the study: October 2005 and June 2006
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Stief 2008 (Continued)

Participants	<p>Inclusion criteria: men aged 45 to 64 years with a history of BPH/LUTS for at least 6 months before commencing the study and an IPSS-total of 12 at screening</p> <p>Exclusion criteria: contraindications to vardenafil, spinal cord injury, prostatitis, history of prostate or bladder cancer, bladder or urethra stricture, urinary retention (postvoid residual (PVR) volume 100 mL), pelvic trauma or surgery, history of any malignancy, life expectancy less than 3 years. Concomitant use of nitrates or NO donors, androgens or antiandrogens, anticoagulants, cytochrome P-450 3A4 inhibitors, and any treatment for ED or alpha-1-adrenoceptor antagonists was prohibited. (Patients receiving alpha-1-adrenoceptor antagonists before the study were eligible to participate, provided they had been on a constant dose for at least the previous month and were willing to withdraw from the medication for the duration of the study.) If alpha-blockers were withdrawn at screening, patients would fail to be eligible for study drug treatment in case of deterioration of any BPH-related symptom during the run-in period (in the opinion of the investigator). Previous or current use of 5-ARI was prohibited. Assessments were carried out four and eight weeks after treatment allocation; maximum treatment duration was 8 weeks. Baseline values for all patients were obtained before treatment (at the end of the run-in period)</p> <p>Total number of participants randomly assigned: 222</p> <p>Mean Age: 55.9 (SD = 5.6) years</p> <p>Mean IPSS-total: 16.8 (SD = 5.1)</p>
Interventions	<p>Intervention(s): vardenafil 10 mg (n = 104)</p> <p>Control(s): placebo (n = 110)</p> <p>Run-in period: 4-week drug-free run-in phase</p> <p>Duration of study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: IPSS total score, maximum urinary flow rate (Qmax)</p> <p>Secondary efficacy: IPSS-storage, IPSS-voiding, PVR urine volume, Benign Prostatic Hyperplasia Quality of Life Questionnaire 9 (Urolife™), IIEF-EF</p> <p>Safety measures: adverse events, laboratory parameters, electrocardiogram (ECG) abnormalities</p>
Notes	<p>This study was sponsored by Bayer Healthcare AG, which was involved in the design, conduct, management, analysis-interpretation of data, preparation, review, and approval of the manuscript. Two of 5 study authors have declared that they acted as speakers and/or consultants for the sponsor; the three remaining study authors were employees of the sponsor</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Low risk	<p>Quote: "randomisation was subsequently performed according to a code generated by the Biometry Administration Group of Global Biometry at Bayer HealthCare, Germany, by using balanced blocks of treatment group allocation and a 1:1 ratio between the two treatment group"</p> <p>Comment: the process adopted for randomisation appears adequate</p>
Allocation concealment (selection bias) All outcomes	Low risk	<p>Quote: "the packaging site was provided with a copy of the randomization code, and investigators received sealed, patient-specific 'code-break' envelopes"</p> <p>Comment: the procedure adopted for allocation concealment appears to be adequate</p>

Stief 2008 (Continued)

Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, and the risk of bias appears to be low
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, and the risk of bias appears to be low
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low, as these outcomes are not susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; registered study NCT00657839 mentions "Masking: Double Blind (Subject, Investigator)" Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail. The risk of bias appears to be low, as these outcomes are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 96/108 (88.8%) in the vardenafil group and 99/113 (87.6%) in the placebo group completed the study. Outcomes have been reported for 104 and 110 participants. However, the risk of bias due to attrition was judged to be unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 96/108 (88.8%) in the vardenafil group and 99/113 (87.6%) in the placebo group completed the study. Adverse events have been reported for 108 and 113 participants. However, the risk of bias due to attrition was judged to be unclear due to considerable loss of post-randomisation data
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 96/108 (88.8%) in the vardenafil group and 99/113 (87.6%) in the placebo group completed the study. The risk of bias due to attrition was judged to be unclear due to considerable loss of post-randomisation data
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: the study was registered at ClinicalTrials.gov (NCT00657839). BPHII and IPSS-QOL were not proposed as outcomes; hence the risk of bias appears to be low

Stief 2008 (Continued)

Selective reporting (re-reporting bias) AE and treatment related harms	Low risk	Comment: adverse events were proposed as outcomes and reported; hence the risk of bias appears to be low
Selective reporting (re-reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: the reported incidence of these outcomes was none. However, the risk of bias was judged to be low
other bias All outcomes	Low risk	Comment: no significant risk of other bias

Takeda 2012

Methods	Study design: randomised double-blind placebo-controlled dose-finding 3-arm parallel-group study Setting: multi-centric Duration of the study: not specified
Participants	Inclusion criteria: men 45 years of age or older with moderate to severe BPH-LUTS (IPSS-total ≥ 13) at the beginning of the 4-week placebo run-in period; bladder outlet obstruction of intermediate severity, defined by Qmax of 4 to 15 mL/s (from a pre-void bladder volume of 150 to 550 mL and a minimum voided volume ≥ 125 mL) and prostate volume > 20 mL Exclusion criteria: PSA > 10.0 ng/mL or between 4.0 and 10.0 ng/mL without clinical judgement of "negative prostate cancer"; postvoid residual volume (PVR) > 300 mL; pelvic surgical procedures on the urinary tract including minimally invasive BPH therapies; clinical evidence of prostate cancer or any bladder or urinary tract conditions that may have affected LUTS; history of significant renal insufficiency; received dutasteride within the previous 6 months. All participants agreed not to use any other treatments for BPH, ED, or overactive bladder (OAB), including α -blockers, 5- α -reductase inhibitors, PDE ₅ inhibitors, or herbal preparations during the study Total number of participants randomly assigned: 422 Median Age: 67.4 years (range not provided) Mean IPSS-total: 16.4 (SD = 6.0)
Interventions	Intervention(s): tadalafil 2.5 mg/d (n = 142); tadalafil 5 mg/d (n = 140) Control(s): placebo (n = 140) Run-in period: 2-week washout period followed by 4-week placebo run-in period Duration of study interventions: 12 weeks
Outcomes	Primary efficacy: change in IPSS-total at 12 weeks Secondary efficacy: change in IPSS-voiding, change in IPSS-storage, change in IPSS-QOL, Qmax Safety measures: frequency and severity of adverse events, vital signs, clinical laboratory tests, PSA level, PVR
Notes	This study was sponsored by Eli Lilly and Company. The sponsor was involved in study design and in collection, analysis, and interpretation of data. Two of the 5 study authors disclosed that they acted

Takeda 2012 (Continued)

as advisory board members for the sponsor; the remaining three study authors were employees of the sponsor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Low risk	Quote: "randomized..... using computer generated random sequence" Comment: random sequence generation appears to be adequate
Allocation concealment (selection bias) All outcomes	Low risk	Quote: "interactive voice response system was used" Comment: the procedure adopted for allocation concealment is adequate
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Blinding of participants and personnel (performance bias) AE and treatment related harms	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Blinding of outcome assessment (detection bias) AE and treatment related harms	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "double-blind"; registered study NCT00783094 mentions "Masking: Double blind (subject, caregiver, investigator, outcomes assessor)" Comment: appears to be adequate
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: 135/142 (95.1%) 2.5 mg tadalafil group, 128/140 (91.4%) tadalafil 5 mg group, and 131/140 (93.6%) placebo group completed the 12-week study period. IPSS-toal and IPSS-QOL were reported for 140/140, 142/142, and 139/140 participants. The risk of bias due to attrition appears to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: 135/142 (95.1%) 2.5 mg tadalafil group, 128/140 (91.4%) tadalafil 5 mg group, and 131/140 (93.6%) placebo group completed the 12-week study period. Safety outcomes have been reported for all randomised participants. The risk of bias due to attrition appears to be low

Takeda 2012 (Continued)

Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: 135/142 (95.1%) 2.5 mg tadalafil group, 128/140 (91.4%) tadalafil 5 mg group, and 131/140 (93.6%) placebo group completed the study. Safety outcomes have been reported for all randomised participants. The risk of bias due to attrition appears to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: these outcomes were proposed in the registered study protocol at ClinicalTrials.gov (NCT00783094) and were reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: these outcomes were proposed in the registered study protocol at ClinicalTrials.gov (NCT00783094) and were reported; hence the risk of bias appears to be low
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: these outcomes were proposed in the registered study protocol at ClinicalTrials.gov (NCT00783094). The reported incidence for these outcomes was none. The risk of bias is low
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant

Tuncel 2010

Methods	Study design: randomised 3-arm parallel-group study Setting: single centre Duration of the study: not mentioned
Participants	Inclusion criteria: men with a clinical diagnosis of ED, Sexual Health Inventory for Males (SHIM) score < 21, IPSS-total score of 12, treatment naïve Exclusion criteria: history of drug use or surgical treatment for BPH and/or ED; prostate biopsy within the last 6 months; use of 5-ARI within 6 months; any urological cancer; previous prostate or bladder/pelvic radiation or surgery; urinary system stone disease; active urinary system infection; acute urinary retention in the last 6 months and, thus, use of urethral catheter for the last year; acute or chronic hepatic failure; acute or chronic renal dysfunction; diagnosis of poorly controlled diabetes mellitus; use of nitrates Total number of participants randomly assigned: 60 Mean Age: 58.8 (range 47 to 77) years Mean IPSS-total: 15.05 (SD = 7.5)
Interventions	Intervention(s): sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg daily (n = 20); sildenafil 25 mg 4 times weekly (n = 20) Control(s): tamsulosin 0.4 mg daily (n = 20) Run-in period: none Duration of study interventions: 8 weeks

Tuncel 2010 (Continued)

Outcomes	Efficacy measures: IPSS-total, third question on IIEF (achieving penetration), fourth question on IIEF (sustaining penetration and erection), SHIM, IPSS-QOL, Qmax, PVR (no classification into primary and secondary efficacy)	
	Safety measures: reported that none dropped out because of side effects	
Notes	No funding source or sponsorship was stated. Conflicts of interest were declared as none	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	Quote: "randomized" Comment: the process of random sequence generation is not described in adequate detail in the Methods section
Allocation concealment (selection bias) All outcomes	Unclear risk	Quote: "randomized"..... allocation concealment is not mentioned Comment: the procedure adopted for allocation concealment is not described in adequate detail in the Methods section
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: no statement Comment: how blinding was exercised is not clear
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	Quote: no statement on blinding Comment: how blinding was exercised is not clear
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: no statement on blinding Comment: how blinding was exercised is not clear; however, these outcome assessments are less susceptible to performance bias
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Quote: no statement on blinding Comment: how blinding was exercised is not clear
Blinding of outcome assessment (detection bias) AE and treatment related harms	Unclear risk	Quote: no statement on blinding Comment: how blinding was exercised is not clear
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: no statement on blinding Comment: how blinding was exercised is not clear; however, these outcome assessments are less susceptible to detection bias
Incomplete outcome data (attrition bias)	Low risk	Comment: IPSS-total and BPHII were reported for 20/20 with sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg daily, 20/20 in sildenafil 25 mg/4 times

Tuncel 2010 (Continued)

IPSS-total, BPHII, IPSS-QOL		weekly, and 20/20 in tamsulosin 0.4 mg daily (n = 20) alone group. The risk of attrition bias was judged to be low
Incomplete outcome data (attrition bias) AE and treatment related harms	Low risk	Comment: all participants completed the study; 20/20 with sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg daily, 20/20 with sildenafil 25 mg/4 times weekly, and 20/20 with tamsulosin 0.4 mg daily (n = 20) alone. The risk of attrition bias was judged to be low
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: outcomes were reported for 20/20 with sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg daily, 20/20 with sildenafil 25 mg/4 times weekly, and 20/20 with tamsulosin 0.4 mg daily (n = 20) alone. No incidence of acute urinary retention or need for surgical intervention. The risk of attrition bias was judged to be low
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: no published study protocol available and study registration could not be traced. BPHII is not an outcome in this study. However, study authors have reported the other standard QOL measure. Therefore, the risk of bias appears to be low
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published study protocol available and study registration could not be traced. The study mentions no dropouts (treatment discontinuations) because of side effects. No adverse events were reported
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published study protocol available and study registration could not be traced. The reported incidence of these outcomes is none; nonetheless, the risk of bias appears to be low
other bias All outcomes	Low risk	Comment: no significant risk of other bias

Yokoyama 2013

Methods	Study design: randomised double-blind placebo-controlled 4-arm parallel-group 12-week study Setting: multi-centre Duration of the study: not specified
Participants	Inclusion criteria: Asian men 45 years of age with > 6-month history of BPH-LUTS, IPSS-total 13, intermediate bladder outlet obstruction per Qmax of 4 to 15 mL/s, prostate volume 20 mL (assessed by ultrasound) Exclusion criteria: PSA > 10.0 ng/mL or 4.0 and 10.0 ng/mL without clinical judgement of "negative prostate cancer"; bladder PVR 300 mL (assessed by ultrasound) or a history of symptomatic orthostatic hypotension; dizziness; vertigo and loss of consciousness or syncope (per warnings in Japanese, Korean, and US tamsulosin prescribing information); clinical evidence of prostate cancer or any bladder or urinary tract condition that might have affected LUTS; treatment with finasteride or dutasteride within 3 and 6 months; history of severe renal or hepatic insufficiency; certain cardiac conditions; nitrate use Total number of participants randomly assigned: 612 Mean Age: 62.8 (SD = 7.7) years MEan IPSS-total: 16.8 (SD = 6.1)

Yokoyama 2013 (Continued)

Interventions	<p>Intervention(s): tadalafil 2.5 mg/d (n = 151); tadalafil 5 mg/d (n = 155); tamsulosin 0.2 mg/d (n = 152)</p> <p>Control(s): placebo (n = 154)</p> <p>Run-in period: 2-week drug-free washout period followed by 4-week single-blind placebo run-in period</p> <p>Duration of study interventions: 12 weeks</p>
Outcomes	<p>Primary efficacy: change in total IPSS with tadalafil 5 mg vs placebo at 12 weeks</p> <p>Secondary efficacy: change in total IPSS with tadalafil 5 mg vs placebo at 2 weeks, 4 weeks, 8 weeks; changes in IPSS-storage, IPSS-voiding, IPSS-QOL, BII, and Qmax from baseline to 12 weeks (tadalafil 2.5 mg/d, 5 mg/d; tamsulosin 0.2 mg/d vs placebo); PGI and CGI at 12 weeks (tadalafil 2.5 mg, 5 mg/d; tamsulosin 0.2 mg/d vs placebo)</p> <p>Safety measures: incidence of TEAEs, clinical laboratory results and vital signs, serum PSA concentration, bladder PVR</p>
Notes	<p>Study was funded by Eli Lilly and Company, the manufacturer of tadalafil. The sponsor was involved in study design, and in collection, analysis, and interpretation of data Two of 7 study authors declared that they were advisory members for the sponsor; three others were employees of the sponsor</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias) All outcomes	Unclear risk	<p>Quote: "randomized"</p> <p>Comment: the process of random sequence generation is not described</p>
Allocation concealment (selection bias) All outcomes	Unclear risk	<p>Quote: "multicentric, randomized, double-blind, placebo-controlled"</p> <p>Comment: the procedure adopted for allocation concealment is not described</p>
Blinding of participants and personnel (performance bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	<p>Quote: "double-blind"</p> <p>Comment: probably done, but who was blinded is not described in adequate detail</p>
Blinding of participants and personnel (performance bias) AE and treatment related harms	Unclear risk	<p>Quote: "double-blind"</p> <p>Comment: probably done, but who was blinded is not described in adequate detail</p>
Blinding of participants and personnel (performance bias) Acute urinary retention and need for surgical intervention	Low risk	<p>Quote: "double-blind"</p> <p>Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low, as these outcomes are not susceptible to performance bias</p>
Blinding of outcome assessment (detection bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	<p>Quote: "double-blind"</p> <p>Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail</p>
Blinding of outcome assessment (detection bias)	Unclear risk	<p>Quote: "double-blind"</p>

Yokoyama 2013 (Continued)

AE and treatment related harms		Comment: probably done, but whether treatment administrator or assessor was blinded is not described in adequate detail
Blinding of outcome assessment (detection bias) Acute urinary retention and need for surgical intervention	Low risk	Quote: "Double-blind" Comment: probably done, but who was blinded is not described in adequate detail. The risk of bias appears to be low, as these outcomes are not susceptible to detection bias
Incomplete outcome data (attrition bias) IPSS-total, BPHII, IPSS-QOL	Unclear risk	Comment: 136/151 (90.1%) with tadalafil 2.5 mg, 137/155 (88.4%) with tadalafil 5 mg, 143/152 (94.1%) with tamsulosin 0.2 mg, and 145/154 (94.2%) with placebo completed the study. Outcomes have been reported for 151, 155, 152 and 154 participants. The risk of bias due to attrition was judged to be unclear due to considerable loss of post-randomisation data with tadalafil 5 mg
Incomplete outcome data (attrition bias) AE and treatment related harms	Unclear risk	Comment: 136/151 (90.1%) with tadalafil 2.5 mg, 137/155 (88.4%) with tadalafil 5 mg, 143/152 (94.1%) with tamsulosin 0.2 mg, and 145/154 (94.2%) with placebo completed the study. Adverse events have been reported for 151, 155, 152 and 154 participants. Risk of bias due to attrition was judged to be unclear due to considerable loss of post-randomisation data with tadalafil 5 mg
Incomplete outcome data (attrition bias) Acute urinary retention and need for surgical intervention	Unclear risk	Comment: 136/151 (90.1%) with tadalafil 2.5 mg, 137/155 (88.4%) with tadalafil 5 mg, 143/152 (94.1%) with tamsulosin 0.2 mg, and 145/154 (94.2%) with placebo completed the study. The risk of bias due to attrition was judged to be unclear
Selective reporting (reporting bias) IPSS-total, BPHII, IPSS-QOL	Low risk	Comment: no published study protocol available and study registration could not be traced; however, the risk of bias appears to be low for these outcomes
Selective reporting (reporting bias) AE and treatment related harms	Low risk	Comment: no published study protocol available and study registration could not be traced; however, the risk of bias appears to be low for these outcomes
Selective reporting (reporting bias) Acute urinary retention and need for surgical intervention	Low risk	Comment: no published study protocol available and study registration could not be traced. However, the risk of bias appears to be low for these outcomes
other bias All outcomes	Unclear risk	Comment: potential risk of bias due to placebo run-in period cannot be ruled out, as it may have enriched the study population with those who were more compliant

5-ARI: 5-alpha reductase inhibitor; AUR: acute urinary retention; BOOI: Bladder Outflow Obstruction Index; BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impact Index; CGI-I: Clinician Global Impression of Improvement; ECG: electrocardiogram; ED: erectile dysfunction; GAQ: Global Assessment Questionnaire; IIEF-EF: International Index of Erectile Function, Erectile Function domain; IPSS: International Prostate Symptom Score; IPSS-QOL: International Prostate Symptom Score-Quality of Life; LUTS: lower urinary tract symptoms; mIPSS: modified IPSS; OAB: overactive bladder; OAB-q SF: Overactive Bladder Questionnaire, Short Form; PDE: phosphodiesterase; PDE₅: phosphodiesterase 5; PdetQmax: voiding pressure; PGI-I: Patient Global Impression of Improvement; PSA: prostate-specific antigen; PVR: post-void residual; Qave: average flow rate; Qmax: maximum flow rate; SAE: serious adverse event; SD: standard deviation; SEP: Sexual Encounter Profile; SHIM: Sexual Health Inventory for Males; TEAE: treatment-emergent adverse event; TSS-BPH: Treatment Satisfaction Scale for BPH; Vcomp: voided volume.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angalakudti 2010	Not a primary RCT but a secondary post hoc analysis of 2 RCTs included in the review
Aurebach 2004	Effect of vardenafil and vardenafil + tamsulosin was evaluated in this study; outcomes for this review were not assessed by this study
Bang 2013	Open-label study
Brock 2013b	Not a primary RCT but a secondary post hoc analysis of 4 RCTs
Broderick 2010	Not a primary RCT but a secondary post hoc analysis of an RCT
Chappel 2015	Not a primary RCT but a secondary post hoc analysis of 4 RCTs
Cho 2011	Open-label study
Chung 2009	Open-label, prospective, non-comparative study
Donatucci 2011	Open-label extension study of an included RCT
Glina 2015	Outcomes for this review were not assessed in this study
Guiliano 2013a	Outcomes for this review were not assessed in this study
Guler 2008	Outcomes for this review were not assessed in this study
Guven 2009	Outcomes for this review were not assessed in this study
Hagberg 2017	Cohort studies with nested case-control analyses
Helmy 2009	Abstract only. No published paper or data could be retrieved
Jin 2011	Outcomes for this review were not assessed in this study
Jin 2013	Not an RCT
Kaplan 2007	Open-label study
Karabakan 2017	Included participants other than BPH-LUTS
Karami 2017	Not a double-blind study
Kraus 2010	Outcomes for this review were not assessed in this RCT
Lee 2011	Outcomes for this review were not assessed in this RCT
Lee 2012	Open-label study
Lee 2013	Not an RCT but a post hoc analysis of another RCT in Korean men
Liguori 2009	Open-label study
Madani 2012	Case-controlled randomised study

Study	Reason for exclusion
Matsukawa 2017	Open-label study
McVary 2008	Open-label study
Nickel 2014	Not a primary RCT but a secondary post hoc analysis of 2 RCTs
Oelke 2014a	Not a primary RCT but a secondary post hoc analysis of 4 RCTs
Oelke 2014b	Not a primary RCT but a secondary post hoc analysis of 2 RCTs
Pinggera 2014	Outcomes for this review were not assessed in this study
Prost 2009	Not a primary study but a secondary post hoc analysis of 2 RCTs
Prost 2013a	Not a primary study but a secondary post hoc analysis of 4 RCTs
Prost 2013b	Not a primary study but a secondary post hoc analysis of 4 RCTs
Roehrborn 2010	Not a primary RCT but a post hoc subgroup analysis of 1 RCT
Sairam 2002	Observational study
Sakalis 2017	The comparator drug solifenacin is not in the purview of this review
Singh 2014	Open-label study
Tamimi 2010	Data could not be retrieved from the study authors
Taneja 2017	Observational study
Ying 2004	Open-label study

BPH-LUTS: benign prostatic hyperplasia-lower urinary tract symptoms; RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Amano 2017](#)

Methods	Efficacy of tadalafil on vessel endothelial function in patients with male LUTS symptoms associated with BPH
Participants	Participants with BPH (n = 81)
Interventions	Tadalafil
Outcomes	Male LUTS parameters: international prostate symptom score (IPSS), overactive bladder symptom score (OABSS), voiding volume, max and mean voiding flow on voiding flowmetry examination, and post-voiding residual urine (RU) were compared at 0, 1, 3, 6, and 12 months Erectile function was evaluated by the sexual health inventory for men (SHIM) score, and vessel endothelial function and peripheral neuropathy were assessed by brachial-ankle pulse wave velocity (baPWV), ankle brachial index (ABI), and vibration perception threshold (VPT) at 0, 3, 6, and 12 months
Notes	

Fukumoto 2017

Methods	Effects of tadalafil on vascular endothelial function and cardiovascular risk in patients with prostatic hyperplasia
Participants	Participants with BPH for whom an α 1-blocker was ineffective (n = 20)
Interventions	Tadalafil
Outcomes	International Prostate Symptom Score, quality of life index, and overactive bladder symptom score Vascular function: change in brachial-ankle pulse wave velocity Vascular endothelial function: change in reactive hyperaemia index
Notes	

Hayashi 2017

Methods	Effects of monotherapy with tadalafil on urinary and sexual function in Japanese men with untreated lower urinary tract symptoms associated with benign prostatic hyperplasia
Participants	Participants with LUTS, who had not received drug therapy for BPH or overactive bladder (OAB), and had an International Prostate Symptom Score (IPSS) > 7 and/or a quality of life (QOL) index > 2
Interventions	Tadalafil was 5 mg once daily
Outcomes	IPSS, QOL, Overactive Bladder Symptom Score (OABSS), maximum urinary flow rate, residual urine volume, International Index of Erectile Function-Erectile Function (IIEF-EF) domain, and Erection Hardness Score (EHS) were evaluated before and 4, 8, and 12 weeks after the start of treatment
Notes	Abstract only; full text not published

Kim 2017

Methods	Phase III multi-centre randomised double-blinded, placebo-controlled clinical trial
Participants	BPH and ED (n = 510)
Interventions	Once-daily fixed-dose combination (FDC) of tamsulosin and tadalafil in comparison to tadalafil monotherapy
Outcomes	IPSS, IIEF, Sexual Encounter Profile, Global Assessment Question, Qmax, PSA, PVR
Notes	

Nagabramanian 2017

Methods	Double-blinded parallel-arm randomised controlled trial
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Nagasubramanian 2017 (Continued)

Participants	Men > 45 years with moderate LUTS, peak flow rate (Qmax) of 5 to 15 mL/s were included. One arm received 0.4 mg tamsulosin only (Group A), and the second group received 5 mg tadalafil with tamsulosin (Group B)
Interventions	Tamsulosin vs combination of tamsulosin and tadalafil
Outcomes	IPSS, IPSS QOL, IIEF-5, Qmax, post-void residual urine (PVRU)
Notes	

Rana 2017

Methods	Prospective randomised study
Participants	Men between 40 and 65 years of age having LUTS, sexually active, and not having coronary artery disease
Interventions	Silodosin (8 mg) vs tadalafil (5 mg) plus silodosin (8 mg)
Outcomes	IPSS and IIEF, adverse events, uroflowmetry, post-void residual urine
Notes	

Sagar 2017

Methods	Prospective randomised comparative study
Participants	Participants with LUTS suggestive of benign prostatic hyperplasia
Interventions	Tadalafil vs tamsulosin
Outcomes	IPSS, BPHII, IPSS-QOL
Notes	

ABI: ankle brachial index; baPWV: brachial-ankle pulse wave velocity; BPH: benign prostatic hyperplasia; BPHII: Benign Prostatic Hyperplasia Impulse Index; ED: erectile dysfunction; EHS: Erection Hardness Score; FDC: fixed-dose combination; IIEF-EF: International Index of Erectile Function, Erectile Function domain; IPSS: International Prostate Symptom Score; IPSS-QOL: International Prostate Symptom Score-Quality of Life; LUTS: lower urinary tract symptoms; OAB: overactive bladder; OABSS: Overactive Bladder Symptom Score; PSA: prostate-specific antigen; PVR: post-void residual; PVRU: post-void residual urine; Qmax: maximum flow; QOL: quality of life; RU: residual urine; SHIM: Sexual Health Inventory for Males; VPT: vibration perception threshold.

Characteristics of ongoing studies [ordered by study ID]

Sharma 2017

Trial name or title	
Methods	Prospective randomised study

Sharma 2017 (Continued)

Participants	With LUTS without erectile dysfunction within the age group of 45 to 65 years and with gland size up to 50 cc with no median lobe involvement, normal upper tract on USG Abdominal and renal function
Interventions	Placebo vs tamsulosin 0.4 mg/d vs tadalafil 10 mg/d vs combination therapy
Outcomes	IPSS, IPSS-QOL, Qmax, PVR
Starting date	NA
Contact information	
Notes	

IPSS: International Prostate Symptom Score; IPSS-QOL: IPSS-Quality of Life; LUTS: lower urinary tract symptoms; NA: not applicable; PVR: post-void residual; Qmax: maximum flow; USG: urine specific gravity.

DATA AND ANALYSES

Comparison 1. PDEI versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IPSS-total	11	4293	Mean Difference (IV, Fixed, 95% CI)	-1.89 [-2.27, -1.50]
2 IPSS-total: subgroup analysis (with or without ED)	3	1816	Mean Difference (IV, Random, 95% CI)	-2.42 [-3.04, -1.80]
2.1 IPSS-total in participants with LUTS and ED	3	1486	Mean Difference (IV, Random, 95% CI)	-2.55 [-3.33, -1.77]
2.2 IPSS-total in participants with LUTS but without ED	1	330	Mean Difference (IV, Random, 95% CI)	-2.10 [-3.39, -0.81]
3 IPSS-total: subgroup analysis (different PDEI)	11	4293	Mean Difference (IV, Fixed, 95% CI)	-1.89 [-2.27, -1.50]
3.1 Tadalafil	9	3738	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-2.20, -1.39]
3.2 Sildenafil	1	341	Mean Difference (IV, Fixed, 95% CI)	-4.4 [-6.96, -1.84]
3.3 Vardenafil	1	214	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-3.57, -0.83]
4 IPSS-total: subgroup analysis (different doses of PDEI)	9	4863	Mean Difference (IV, Random, 95% CI)	-1.96 [-2.41, -1.52]
4.1 Tadalafil 2.5 mg/d	4	1396	Mean Difference (IV, Random, 95% CI)	-1.31 [-2.19, -0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Tadalafil 5 mg/d	8	2452	Mean Difference (IV, Random, 95% CI)	-1.88 [-2.33, -1.42]
4.3 Tadalafil 10 mg/d	1	426	Mean Difference (IV, Random, 95% CI)	-3.43 [-4.79, -2.07]
4.4 Tadalafil 20 mg/d	2	589	Mean Difference (IV, Random, 95% CI)	-3.29 [-4.44, -2.14]
5 IPSS-total: sensitivity analysis (RCT without run-in period excluded)	8	3567	Mean Difference (IV, Fixed, 95% CI)	-1.71 [-2.12, -1.29]
6 BPHII	7	3646	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.71, -0.33]
7 BPHII: subgroup analysis (with or without ED)	3	1809	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-0.99, -0.43]
7.1 IPSS-BPHII score - in participants with LUTS and ED	3	1480	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-1.12, -0.49]
7.2 IPSS-BPHII score - in participants with LUTS but no ED	1	329	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.98, 0.18]
8 BPHII: subgroup analysis (different PDEI)	7	3878	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.71, -0.33]
8.1 Tadalafil	6	3527	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.70, -0.31]
8.2 Sildenafil	1	351	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-2.11, -0.09]
8.3 Vardenafil	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 BPHII: subgroup analysis (different doses of PDEI)	6	4502	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.61, -0.29]
9.1 Tadalafil 2.5 mg/d	3	1097	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.61, 0.04]
9.2 Tadalafil 5 mg/d	6	2561	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.69, -0.28]
9.3 Tadalafil 10 mg/d	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.15, -0.01]
9.4 Tadalafil 20 mg/d	1	418	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.20, -0.04]
10 Any AE with short-term use	11	4386	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.21, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Any AE with short-term use: subgroup analysis (with or without ED)	2	1458	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.21, 1.76]
11.1 Participants with ED	2	1120	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.11, 1.68]
11.2 Participants without ED	1	338	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.33, 2.24]
12 Any AE with short-term use: subgroup analysis (different PDEI)	11	4386	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.21, 1.67]
12.1 Tadalafil	9	3796	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.19, 1.75]
12.2 Sildenafil	1	369	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.99, 1.51]
12.3 Vardenafil	1	221	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.11, 3.11]
13 Any AE with short-term use: subgroup analysis (different doses of PDEI)	9	4923	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.25, 1.62]
13.1 Tadalafil 2.5 mg/d	4	1405	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.03, 1.46]
13.2 Tadalafil 5 mg/d	8	2471	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.12, 1.63]
13.3 Tadalafil 10 mg/d	1	427	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.19, 2.24]
13.4 Tadalafil 20 mg/d	2	620	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.53, 2.44]
14 Any AE with short-term use: sensitivity analysis (RCT without run-in period excluded)	8	3596	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.13, 1.65]
15 IPSS-QOL	9	3920	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.35, -0.16]
16 IPSS-QOL: subgroup analysis (with or without ED)	3	1815	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.60, -0.21]
16.1 IPSS-QOL in participants with LUTS and ED	3	1486	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.62, -0.20]
16.2 IPSS-QOL in participants with LUTS but no ED	1	329	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.98, 0.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 IPSS-QOL: subgroup analysis (different PDEI)	9	3920	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.35, -0.16]
17.1 Tadalafil	8	3569	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.34, -0.15]
17.2 Sildenafil	1	351	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-1.18, -0.18]
17.3 Vardenafil	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 IPSS-QOL: subgroup analysis (different doses of PDEI)	8	4686	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.35, -0.19]
18.1 Tadalafil 2.5 mg/d	4	1390	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.34, -0.02]
18.2 Tadalafil 5 mg/d	8	2452	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.38, -0.18]
18.3 Tadalafil 10 mg/d	1	426	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.71, -0.13]
18.4 Tadalafil 20 mg/d	1	418	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.69, -0.09]
19 IPSS-QOL: sensitivity analysis (RCT without run-in period excluded)	8	3569	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.34, -0.15]
20 Other treatment-related harms: AE with short-term use related to vasodilatation	11	4386	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.18, 1.76]
21 Other treatment-related harms: AE with short-term use related to body pain	10	4017	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [1.98, 5.98]
22 Other treatment-related harms: AE with short-term use related to upper GI tract	8	2995	Risk Ratio (M-H, Fixed, 95% CI)	14.19 [5.80, 34.72]
23 Other treatment-related harms: AE with short-term use leading to treatment discontinuation	10	4165	Risk Ratio (M-H, Fixed, 95% CI)	2.20 [1.38, 3.51]

Analysis 1.1. Comparison 1 PDEI versus placebo, Outcome 1 IPSS-total.

Analysis 1.2. Comparison 1 PDEI versus placebo, Outcome 2 IPSS-total: subgroup analysis (with or without ED).

Analysis 1.3. Comparison 1 PDEI versus placebo, Outcome 3 IPSS-total: subgroup analysis (different PDEI).

Analysis 1.4. Comparison 1 PDEI versus placebo, Outcome 4 IPSS-total: subgroup analysis (different doses of PDEI).

Analysis 1.5. Comparison 1 PDEI versus placebo, Outcome 5 IPSS- total: sensitivity analysis (RCT without run-in period excluded).

Analysis 1.6. Comparison 1 PDEI versus placebo, Outcome 6 BPHII.

Analysis 1.7. Comparison 1 PDEI versus placebo, Outcome 7 BPHII: subgroup analysis (with or without ED).

Analysis 1.8. Comparison 1 PDEI versus placebo, Outcome 8 BPHII: subgroup analysis (different PDEI).

Analysis 1.9. Comparison 1 PDEI versus placebo, Outcome 9 BPHII: subgroup analysis (different doses of PDEI).

Analysis 1.10. Comparison 1 PDEI versus placebo, Outcome 10 Any AE with short-term use.

Analysis 1.11. Comparison 1 PDEI versus placebo, Outcome 11 Any AE with short-term use: subgroup analysis (with or without ED).

Analysis 1.12. Comparison 1 PDEI versus placebo, Outcome 12 Any AE with short-term use: subgroup analysis (different PDEI).

Analysis 1.13. Comparison 1 PDEI versus placebo, Outcome 13 Any AE with short-term use: subgroup analysis (different doses of PDEI).

Analysis 1.14. Comparison 1 PDEI versus placebo, Outcome 14 Any AE with short-term use: sensitivity analysis (RCT without run-in period excluded).

Analysis 1.15. Comparison 1 PDEI versus placebo, Outcome 15 IPSS-QOL.

Analysis 1.16. Comparison 1 PDEI versus placebo, Outcome 16 IPSS-QOL: subgroup analysis (with or without ED).

Analysis 1.17. Comparison 1 PDEI versus placebo, Outcome 17 IPSS-QOL: subgroup analysis (different PDEI).

Analysis 1.18. Comparison 1 PDEI versus placebo, Outcome 18 IPSS-QOL: subgroup analysis (different doses of PDEI).

Analysis 1.19. Comparison 1 PDEI versus placebo, Outcome 19 IPSS-QOL: sensitivity analysis (RCT without run-in period excluded).

Analysis 1.20. Comparison 1 PDEI versus placebo, Outcome 20 Other treatment-related harms: AE with short-term use related to vasodilatation.

Analysis 1.21. Comparison 1 PDEI versus placebo, Outcome 21 Other treatment-related harms: AE with short-term use related to body pain.

Analysis 1.22. Comparison 1 PDEI versus placebo, Outcome 22 Other treatment-related harms: AE with short-term use related to upper GI tract.

Analysis 1.23. Comparison 1 PDEI versus placebo, Outcome 23 Other treatment-related harms: AE with short-term use leading to treatment discontinuation.

Comparison 2. PDEI versus AB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IPSS-total	4	933	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.49, 0.93]
2 IPSS-total: subgroup analysis (different PDEI)	4	782	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.58, 0.95]
2.1 Tadalafil	3	742	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.65, 0.91]
2.2 Sildenafil	1	40	Mean Difference (IV, Fixed, 95% CI)	1.40 [-2.24, 5.04]
3 IPSS-total: subgroup analysis (different doses of PDEI)	4	1085	Mean Difference (IV, Random, 95% CI)	0.35 [-0.28, 0.98]
3.1 Tadalafil 5 mg/d vs tamsulosin 0.4 mg/d	1	336	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.98, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Tadalafil 5 mg/d vs tamsulosin 0.2 mg/d	2	406	Mean Difference (IV, Random, 95% CI)	0.42 [-0.68, 1.51]
3.3 Tadalafil 2.5 mg/d vs tamsulosin 0.2 mg/d	1	303	Mean Difference (IV, Random, 95% CI)	0.70 [-0.41, 1.81]
3.4 Sildenafil 25 mg administered 4 times a week vs tamsulosin 0.4 mg/d	1	40	Mean Difference (IV, Random, 95% CI)	1.40 [-2.24, 5.04]
4 IPSS-total: sensitivity analysis (RCT without run-in period excluded)	3	742	Mean Difference (IV, Random, 95% CI)	0.07 [-0.88, 1.02]
5 BPHII	2	550	Mean Difference (IV, Random, 95% CI)	0.03 [-1.10, 1.16]
6 BPHII: subgroup analysis (different PDEI)	2	403	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.23, 0.69]
6.1 Tadalafil	2	403	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.23, 0.69]
7 BPHII: subgroup analysis (different doses of PDEI)	2	700	Mean Difference (IV, Random, 95% CI)	0.24 [-0.40, 0.88]
7.1 Tadalafil 5 mg/d vs tamsulosin 0.2 mg/d	2	403	Mean Difference (IV, Random, 95% CI)	0.04 [-1.13, 1.21]
7.2 Tadalafil 2.5 mg/d vs tamsulosin 0.2 mg/d	1	297	Mean Difference (IV, Random, 95% CI)	0.5 [-0.06, 1.06]
8 BPHII: sensitivity analysis (RCT without run-in period excluded)	2	550	Mean Difference (IV, Random, 95% CI)	0.03 [-1.10, 1.16]
9 Any AE with short-term use	4	936	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.80, 2.30]
10 IPSS-QOL	4	933	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.48, 0.29]
11 IPSS-QOL: subgroup analysis (different PDEIs)	4	782	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.19, 0.17]
11.1 Tadalafil	3	742	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.16, 0.21]
11.2 Sildenafil	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-1.78, 0.18]
12 IPSS-QOL: subgroup analysis (different doses of PDEI)	4	1085	Mean Difference (IV, Random, 95% CI)	0.01 [-0.29, 0.32]
12.1 Tadalafil 5 mg/d vs tamsulosin 0.4 mg/d	1	336	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.48, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Tadalafil 5 mg/d vs tamsulosin 0.2 mg/d	2	406	Mean Difference (IV, Random, 95% CI)	0.11 [-0.37, 0.59]
12.3 Tadalafil 2.5 mg/d vs tamsulosin 0.2 mg/d	1	303	Mean Difference (IV, Random, 95% CI)	0.30 [0.02, 0.58]
12.4 Sildenafil 25 mg/d vs tamsulosin 0.4 mg/d	1	40	Mean Difference (IV, Random, 95% CI)	-0.8 [-1.78, 0.18]
13 IPSS-QOL: sensitivity analysis (RCT without run-in period excluded)	3	742	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.38, 0.36]
14 Other treatment-related harms: AE with short-term use related to vasodilatation	3	746	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [1.05, 5.56]
15 Other treatment-related harms: AE with short-term use related to body pain	3	747	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.38, 8.18]
16 Other treatment-related harms: AE with short-term use related to upper GI tract	3	746	Risk Ratio (M-H, Fixed, 95% CI)	4.87 [0.58, 41.22]
17 Other treatment-related harms: AE with short-term use leading to treatment discontinuation	4	786	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.31, 5.05]

Analysis 2.1. Comparison 2 PDEI versus AB, Outcome 1 IPSS-total.

Analysis 2.2. Comparison 2 PDEI versus AB, Outcome 2 IPSS-total: subgroup analysis (different PDEI).

Analysis 2.3. Comparison 2 PDEI versus AB, Outcome 3 IPSS-total: subgroup analysis (different doses of PDEI).

Study or subgroup	[PDEI]		[Alfa Blocker]		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Test for overall effect: Z=1.1(P=0.27)							
Test for subgroup differences: Chi²=2.52, df=1 (P=0.47), I²=0%							

Analysis 2.4. Comparison 2 PDEI versus AB, Outcome 4 IPSS- total: sensitivity analysis (RCT without run-in period excluded).

Study or subgroup	[PDEI]		[Alfa Blocker]		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Kim 2011	51	-5.8 (4.3)	49	-5.4 (4.9)		22.26%	-0.4[-2.2,1.4]
Oelke 2012	171	-6.3 (6.5)	165	-5.7 (6.4)		33.2%	-0.6[-1.98,0.78]
Yokoyama 2013	154	-4.7 (5)	152	-5.5 (4.9)		44.54%	0.8[-0.31,1.91]
Total ***	376		366			100%	0.07[-0.88,1.02]
Heterogeneity: $\text{Tau}^2=0.21$; $\text{Chi}^2=2.8, \text{df}=2(P=0.25)$; $I^2=28.67\%$							
Test for overall effect: $Z=0.14(P=0.89)$							

Analysis 2.5. Comparison 2 PDEI versus AB, Outcome 5 BPHII.

Study or subgroup	[PDEI]		[Alfa Blocker]		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Kim 2011	51	-2.2 (2.1)	49	-1.6 (2.1)		45.57%	-0.6[-1.43,0.23]
Yokoyama 2013	300	-1 (2.5)	150	-1.6 (2.4)		54.43%	0.56[0.08,1.04]
Total ***	351		199			100%	0.03[-1.1,1.16]
Heterogeneity: $\text{Tau}^2=0.55$; $\text{Chi}^2=5.63, \text{df}=1(P=0.02)$; $I^2=82.25\%$							
Test for overall effect: $Z=0.05(P=0.96)$							

Analysis 2.6. Comparison 2 PDEI versus AB, Outcome 6 BPHII: subgroup analysis (different PDEI).

Study or subgroup	[PDEI]		[Alfa Blocker]		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.6.1 Tadalafil							
Kim 2011	51	-2.2 (2.1)	49	-1.6 (2.1)		30.78%	-0.6[-1.43,0.23]
Yokoyama 2013	153	-1 (2.5)	150	-1.6 (2.4)		69.22%	0.6[0.05,1.15]
Subtotal ***	204		199			100%	0.23[-0.23,0.69]
Heterogeneity: Tau²=0; Chi²=5.57, df=1(P=0.02); I²=82.05%							
Test for overall effect: Z=0.98(P=0.33)							
Total ***	204		199			100%	0.23[-0.23,0.69]
Heterogeneity: Tau²=0; Chi²=5.57, df=1(P=0.02); I²=82.05%							
Test for overall effect: Z=0.98(P=0.33)							

Analysis 2.7. Comparison 2 PDEI versus AB, Outcome 7 BPHII: subgroup analysis (different doses of PDEI).

Analysis 2.8. Comparison 2 PDEI versus AB, Outcome 8 BPHII: sensitivity analysis (RCT without run-in period excluded).

Analysis 2.9. Comparison 2 PDEI versus AB, Outcome 9 Any AE with short-term use.

Analysis 2.10. Comparison 2 PDEI versus AB, Outcome 10 IPSS-QOL.

Analysis 2.11. Comparison 2 PDEI versus AB, Outcome 11 IPSS-QOL: subgroup analysis (different PDEIs).

Analysis 2.12. Comparison 2 PDEI versus AB, Outcome 12 IPSS-QOL: subgroup analysis (different doses of PDEI).

Analysis 2.13. Comparison 2 PDEI versus AB, Outcome 13 IPSS-QOL: sensitivity analysis (RCT without run-in period excluded).

Analysis 2.14. Comparison 2 PDEI versus AB, Outcome 14 Other treatment-related harms: AE with short-term use related to vasodilatation.

Analysis 2.15. Comparison 2 PDEI versus AB, Outcome 15 Other treatment-related harms: AE with short-term use related to body pain.

Analysis 2.16. Comparison 2 PDEI versus AB, Outcome 16 Other treatment-related harms: AE with short-term use related to upper GI tract.

Analysis 2.17. Comparison 2 PDEI versus AB, Outcome 17 Other treatment-related harms: AE with short-term use leading to treatment discontinuation.

Comparison 3. PDEI + AB versus AB alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IPSS-total	4	193	Mean Difference (IV, Fixed, 95% CI)	-2.56 [-3.92, -1.19]
2 IPSS-total: subgroup analysis (different PDEI)	4	193	Mean Difference (IV, Fixed, 95% CI)	-2.56 [-3.92, -1.19]
2.1 Tadalafil	2	94	Mean Difference (IV, Fixed, 95% CI)	-3.02 [-4.83, -1.22]
2.2 Sildenafil	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.56, 3.56]
2.3 Vardenafil	1	59	Mean Difference (IV, Fixed, 95% CI)	-2.18 [-4.53, 0.17]
3 IPSS-total: subgroup analysis (different doses of PDEI)	4	193	Mean Difference (IV, Random, 95% CI)	-2.56 [-3.92, -1.19]
3.1 Tadalafil 5 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	40	Mean Difference (IV, Random, 95% CI)	-3.70 [-6.44, -0.96]
3.2 Tadalafil 20 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	54	Mean Difference (IV, Random, 95% CI)	-2.50 [-4.91, -0.09]
3.3 Vardenafil 10 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	59	Mean Difference (IV, Random, 95% CI)	-2.18 [-4.53, 0.17]
3.4 Sildenafil 25 mg + tamsulosin 0.4 mg 4 times weekly vs tamsulosin 0.4 mg/d	1	40	Mean Difference (IV, Random, 95% CI)	-1.0 [-5.56, 3.56]
4 IPSS-total: sensitivity analysis (RCTs without placebo run-in period excluded)	2	113	Mean Difference (IV, Random, 95% CI)	-2.34 [-4.02, -0.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Any AE in short-term use	4	194	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.53, 5.17]
6 Any AE in short-term use: subgroup analysis (different PDEI)	4	194	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.53, 5.17]
6.1 Tadalafil	2	94	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [1.30, 6.90]
6.2 Sildenafil	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Vardenafil	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.6 [1.06, 6.39]
7 Any AE with short-term use: subgroup analysis (different doses of PDEI)	4	194	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.53, 5.17]
7.1 Tadalafil 5 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
7.2 Tadalafil 20 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [1.27, 7.09]
7.3 Vardenafil 5 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.6 [1.06, 6.39]
7.4 Sildenafil 25 mg + tamsulosin 0.4 mg 4 times weekly vs tamsulosin 0.4 mg daily	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Any AE with short-term use: sensitivity analysis (RCT without run-in period excluded)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	2.8 [1.50, 5.21]
9 IPSS-QOL	2	94	Mean Difference (IV, Fixed, 95% CI)	-1.08 [-1.92, -0.23]
10 IPSS-QOL: subgroup analysis (different PDEIs)	2	94	Mean Difference (IV, Fixed, 95% CI)	-1.08 [-1.92, -0.23]
10.1 Tadalafil	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-2.40, 1.00]
10.2 Sildenafil	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-2.18, -0.22]
10.3 Vardenafil	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 IPSS-QOL: subgroup analysis (different doses of PDEI)	2	94	Mean Difference (IV, Random, 95% CI)	-1.08 [-1.92, -0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Sildenafil 25 mg + tamsulosin 0.4 mg 4 times weekly vs tamsulosin 0.4 mg/d	1	40	Mean Difference (IV, Random, 95% CI)	-1.2 [-2.18, -0.22]
11.2 Tadalafil 20 mg + tamsulosin 0.4 mg/d vs tamsulosin 0.4 mg/d	1	54	Mean Difference (IV, Random, 95% CI)	-0.7 [-2.40, 1.00]
12 IPSS-QOL: sensitivity analysis (RCT without placebo run-in period excluded)	1	54	Mean Difference (IV, Random, 95% CI)	-0.7 [-2.40, 1.00]
13 Other treatment-related harms: AE with short-term use related to vasodilatation	3	154	Risk Ratio (M-H, Fixed, 95% CI)	4.8 [1.93, 11.91]
14 Other treatment-related harms: AE with short-term use related to upper GI tract	4	194	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.75, 48.30]
15 Other treatment-related harms: AE with short-term use leading to treatment discontinuation	3	154	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.53]

Analysis 3.1. Comparison 3 PDEI + AB versus AB alone, Outcome 1 IPSS-total.

Study or subgroup	[PDEI + alpha Blocker]		[alpha Blocker alone]		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Bechara 2008	27	-9.2 (5.1)	27	-6.7 (3.9)		32.17%	-2.5[-4.91,-0.09]
Gacci 2012	30	-5.8 (5.2)	29	-3.6 (4)		33.91%	-2.18[-4.53,0.17]
Regadas 2013	20	-9.7 (5.1)	20	-6 (3.6)		24.94%	-3.7[-6.44,-0.96]
Tuncel 2010	20	-6.3 (8)	20	-5.3 (6.7)		8.98%	-1[-5.56,3.56]
Total ***	97		96			100%	-2.56[-3.92,-1.19]
Heterogeneity: Tau ² =0; Chi ² =1.22, df=3(P=0.75); I ² =0%							
Test for overall effect: Z=3.67(P=0)							
					<div style="display: flex; justify-content: space-between; width: 100%;"> [PDEI+alpha Bl better] -10 -5 0 5 10 [alpha Bl alone better] </div>		

Analysis 3.2. Comparison 3 PDEI + AB versus AB alone, Outcome 2 IPSS-total: subgroup analysis (different PDEI).

Study or subgroup	[PDEI + alpha blocker]		[alpha blocker alone]		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
3.2.1 Tadalafil							
Bechara 2008	27	-9.2 (5.1)	27	-6.7 (3.9)		32.17%	-2.5[-4.91,-0.09]
Regadas 2013	20	-9.7 (5.1)	20	-6 (3.6)		24.94%	-3.7[-6.44,-0.96]
Subtotal ***	47		47			57.11%	-3.02[-4.83,-1.22]
Heterogeneity: Tau ² =0; Chi ² =0.42, df=1(P=0.52); I ² =0%							
Test for overall effect: Z=3.28(P=0)							
					<div style="display: flex; justify-content: space-between; width: 100%;"> [PDEI+alpha bl better] -10 -5 0 5 10 [alpha bl alone better] </div>

Analysis 3.3. Comparison 3 PDEI + AB versus AB alone, Outcome 3 IPSS-total: subgroup analysis (different doses of PDEI).

Analysis 3.4. Comparison 3 PDEI + AB versus AB alone, Outcome 4 IPSS-total: sensitivity analysis (RCTs without placebo run-in period excluded).

Analysis 3.5. Comparison 3 PDEI + AB versus AB alone, Outcome 5 Any AE in short-term use.

Analysis 3.6. Comparison 3 PDEI + AB versus AB alone, Outcome 6 Any AE in short-term use: subgroup analysis (different PDEI).

Analysis 3.7. Comparison 3 PDEI + AB versus AB alone, Outcome 7 Any AE with short-term use: subgroup analysis (different doses of PDEI).

Analysis 3.8. Comparison 3 PDEI + AB versus AB alone, Outcome 8 Any AE with short-term use: sensitivity analysis (RCT without run-in period excluded).

Analysis 3.9. Comparison 3 PDEI + AB versus AB alone, Outcome 9 IPSS-QOL.

Analysis 3.10. Comparison 3 PDEI + AB versus AB alone, Outcome 10 IPSS-QOL: subgroup analysis (different PDEIs).

Analysis 3.11. Comparison 3 PDEI + AB versus AB alone, Outcome 11 IPSS-QOL: subgroup analysis (different doses of PDEI).

Analysis 3.12. Comparison 3 PDEI + AB versus AB alone, Outcome 12 IPSS-QOL: sensitivity analysis (RCT without placebo run-in period excluded).

Analysis 3.13. Comparison 3 PDEI + AB versus AB alone, Outcome 13 Other treatment-related harms: AE with short-term use related to vasodilatation.

Analysis 3.14. Comparison 3 PDEI + AB versus AB alone, Outcome 14 Other treatment-related harms: AE with short-term use related to upper GI tract.

Analysis 3.15. Comparison 3 PDEI + AB versus AB alone, Outcome 15 Other treatment-related harms: AE with short-term use leading to treatment discontinuation.

Comparison 4. PDEI + AB versus PDEI alone

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 IPSS-total	1	40	Mean Difference (IV, Random, 95% CI)	-2.40 [-6.47, 1.67]
2 IPSS-QOL	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.80, 1.00]

Analysis 4.1. Comparison 4 PDEI + AB versus PDEI alone, Outcome 1 IPSS-total.

Analysis 4.2. Comparison 4 PDEI + AB versus PDEI alone, Outcome 2 IPSS-QOL.

Comparison 5. PDEI + 5-ARI versus 5-ARI alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IPSS-total	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 at 4 weeks	1	695	Mean Difference (IV, Random, 95% CI)	-2.0 [-2.84, -1.16]
1.2 at 12 weeks	1	695	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.24, -0.56]
1.3 at 26 weeks	1	695	Mean Difference (IV, Random, 95% CI)	-1.0 [-1.83, -0.17]
2 IPSS-QOL	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 at 4 weeks	1	695	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.58, -0.02]
2.2 at 12 weeks	1	695	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.48, 0.08]
2.3 at 26 weeks	1	695	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.48, 0.08]
3 Any AE with long-term use (26 weeks)	1	695	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.84, 1.36]
4 Other treatment-related harms: AE with long-term use (26 weeks) related to vasodilatation	1	696	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
5 Other treatment-related harms: AE with long-term use (26 weeks) related to body pain	1	696	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.07, 6.81]
6 Other treatment-related harms: AE with long-term use (26 weeks) related to upper GI tract	1	696	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [0.87, 18.92]
7 Other treatment-related harms: AE with long-term use (26 weeks) leading to treatment discontinuation	1	696	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.21, 1.91]
8 Other treatment-related harms: AE with long-term use (26 weeks) related to sexual function	1	696	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.17, 1.46]

Analysis 5.1. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 1 IPSS-total.

Analysis 5.2. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 2 IPSS-QOL.

Analysis 5.3. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 3 Any AE with long-term use (26 weeks).

Analysis 5.4. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 4 Other treatment-related harms: AE with long-term use (26 weeks) related to vasodilatation.

Analysis 5.5. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 5 Other treatment-related harms: AE with long-term use (26 weeks) related to body pain.

Analysis 5.6. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 6 Other treatment-related harms: AE with long-term use (26 weeks) related to upper GI tract.

Analysis 5.7. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 7 Other treatment-related harms: AE with long-term use (26 weeks) leading to treatment discontinuation.

Analysis 5.8. Comparison 5 PDEI + 5-ARI versus 5-ARI alone, Outcome 8 Other treatment-related harms: AE with long-term use (26 weeks) related to sexual function.

ADDITIONAL TABLES

Table 1. Description of interventions

Study (year)	Intervention(s) (route, frequency, total dose/d)	Intervention(s) appropriate as applied in a clinical practice setting ^a (description)	Comparator(s) (route, frequency, total dose/d)	Comparator(s) appropriate as applied in a clinical practice setting ^a (description)
Casabe (2014)	I1: tadalafil 5 mg/d + finasteride 5 mg/d oral	Tadalafil and finasteride were used in this study as per clinical practice setting	C1: placebo + finasteride 5 mg/d oral	Finasteride was used in this study as per clinical practice setting

Table 1. Description of interventions (Continued)

				Placebo; N/CPS
Regadas (2013)	I1: tadalafil 5 mg/d + tamsulosin 0.4 mg/d oral	Tadalafil and tamsulosin were used in this study as per clinical practice setting	C1: tamsulosin 0.4 mg/d + placebo oral	Tamsulosin was used in this study as per clinical practice setting Placebo; N/CPS
Brock (2013a)	I1: tadalafil 5 mg/d oral	Tadalafil was used in this study as per clinical practice setting	C1: placebo once daily oral	N/CPS
Yokoyama (2013)	I1: tadalafil 2.5 mg/d oral I2: tadalafil 5 mg/d oral I3: tamsulosin 0.2 mg/d oral	Tadalafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
Egerdie (2012)	I1: tadalafil 2.5 mg/d oral I2: tadalafil 5 mg/d oral	Tadalafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
Gacci (2012)	I1: tamsulosin 0.4 mg/d + vardenafil 10 mg/d oral	Tadalafil and vardenafil were used in this study as per clinical practice setting	C1: tamsulosin 0.4 mg/d oral	Tamsulosin was used in this study as per clinical practice setting
Oelke (2012)	I1: tadalafil 5 mg/d oral I2: tamsulosin 0.4 mg/d oral	Tadalafil and tamsulosin were used in this study as per clinical practice setting	C1: placebo oral	N/CPS
Takeda (2012)	I1: tadalafil 2.5 mg/d oral I2: tadalafil 5 mg/d oral	Tadalafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
Kim (2011)	I1: tadalafil 5 mg/d oral	Tadalafil and tamsulosin were used in this study as per clinical practice setting	C1: placebo oral	N/CPS

Table 1. Description of interventions (Continued)

	I2: tamsulosin 0.2 mg/d			
	oral			
Dmochowski (2010)	I1: tamsulosin 20 mg/d oral	Tadalafil is approved for use in BPH-LUTS at 2.5 mg and 5 mg per day Tadalafil dose used in this study is higher than that used in the clinical practice setting	C1: placebo oral	N/CPS
Prost (2011)	I1: tadalafil 5 mg/d oral	Tadalafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
Tuncel (2010)	I1: sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg/d oral I2: sildenafil 25 mg/4 times weekly oral	Sildenafil and tamsulosin were used in this study as per clinical practice setting	C1: tamsulosin 0.4 mg/d oral	Tamsulosin was used in this study as per clinical practice setting
Bechara (2008)	I1: tadalafil 20 mg/d + tamsulosin 0.4 mg/d oral	Tadalafil is approved for use in BPH-LUTS at 2.5 mg and 5 mg per day Tadalafil dose used in this study is higher than that used in clinical practice setting Tamsulosin was used in this study as per clinical practice setting	C1: tamsulosin 0.4 mg/d + placebo oral	Tamsulosin was used in this study as per clinical practice setting Placebo; N/CPS
	I2: tamsulosin 0.4 mg/d + placebo oral	Tamsulosin was used in this study as per clinical practice setting For placebo; N/CPS	C2: tadalafil 20 mg/d + tamsulosin 0.4 mg/d oral	Tadalafil is approved for use in BPH-LUTS at 2.5 mg and 5 mg per day Tadalafil dose used in this study was higher than that used in clinical practice setting Tamsulosin was used in this study as per clinical practice setting
Roehrborn (2008)	I1: tadalafil 2.5 mg/d oral I2: tadalafil 5 mg/d oral I3: tadalafil 10 mg/d oral	Tadalafil is approved for use in BPH-LUTS at 2.5 mg and 5 mg per day This is a dose-ranging study; tadalafil doses used in this study for I3 and I4 were higher than those used in clinical practice setting	C1: placebo oral	N/CPS

Table 1. Description of interventions (Continued)

	I4: tadalafil 20 mg/d			
	oral			
Stief (2008)	I1: vardenafil 10 mg	Vardenafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
McVary (2007a)	I1: sildenafil 50 to 100 mg/d	Sildenafil was used in this study as per clinical practice setting	C1: placebo oral	N/CPS
	oral			
McVary (2007b)	I1: tadalafil 5 to 20 mg/d	Tadalafil dose used in this study in the dose escalation phase was higher than that used in clinical practice setting	C1: placebo oral	N/CPS
	oral			

^aThe term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision for contraindications, and other important features).

BPH: benign prostatic hyperplasia; C: comparator; I: intervention; LUTS: lower urinary tract symptoms; N/CPS: no specification of clinical practice setting possible.

Table 2. Baseline characteristics

Study (year)	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up) (days, months, years...)	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of disease (mean/range years (SD), or as reported)
Casabe (2014)	I1: tadalafil 5 mg/d + finasteride 5 mg/d	12 weeks (for primary endpoint)	Men > 45 years with BPH-LUTS; IPSS ≥ 13 Qmax 4 to 15 mL/s	November 2010 to September 2012	USA, Canada, Latin America	-	Whites (85.5%)	-
	C1: placebo + finasteride 5 mg/d	Study continued maintaining blinding until 26 weeks (for secondary endpoints)	Prostatic volume ≥ 30 cc Naive to 5-ARI therapy				Black/African American (10.1%) Native American (2.5%) Other (3.9%)	
Regadas (2013)	I1: tadalafil 5 mg/d + tamsulosin 0.4 mg/d C1: tamsulosin 0.4 mg/d + placebo	30 days	Men > 45 years, BOOI > 20 IPSS > 14	October 2010 to September 2011	"-"	-	"-"	-
Brock (2013a)	I1: tadalafil 5 mg/d C1: placebo	12 weeks	Men ≥ 45 years BPH-LUTS > 6 months IPSS ≥ 13 Qmax 4 to 15 mL/s	"-"	-	-	-	-
Yokoyama (2013)	I1: tadalafil 2.5 mg/d	12 weeks	Men > 45 years; BPH-LUTS > 6 months IPSS > 13 Qmax 4 to 15 mL/s	"-"	Japan	-	Japan (55.8%)	-
	I2: tadalafil 5 mg/d				Korea Taiwan		Korea (29.1%)	

Table 2. Baseline characteristics (Continued)

	I3: tamsulosin 0.2 mg/d		Prostate volume > 20 cc				Taiwan (14.8%)	
	C1: placebo							
Egerdie (2012)	I1: tadalafil 2.5 mg/d	12 weeks	Men ≥ 45 years, ≥ 3 months h/o ED, ≥ 6 months h/o BPH-LUTS (LUTS + ED)		Europe	-	White (93%)	-
	I2: tadalafil 5 mg/d				Mexico		Black American (4%)	
					USA/Canada		Asian (2.5%)	
	C2: placebo						Hispanic (15%)	
							Other (0.6%)	
Gacci (2012)	I1: tamsulosin 0.4 mg/d	12 weeks	Men with persistent storage/irritative symptoms after tamsulosin 0.4 mg treatment for 2 weeks; IPSS-storage ≥ 8	"-"	"-"	-	"-"	-
	+ vardenafil 10 mg/d							
	C1: tamsulosin 0.4 mg/d							
Oelke (2012)	I1: tadalafil 5 mg/d	12 weeks	Men ≥ 45 years, BPH-LUTS > 6 months, IPSS ≥ 13, Qmax 4 to 15 mL/s before placebo lead-in period	December 2009 to January 2011	Australia, Austria, Belgium, France, Germany, Greece, Italy, Mexico, The Netherlands, Poland	-	White (76%)	-
	I2: tamsulosin 0.4 mg/d						Black or African American (0.3%)	
							American Indian/Alaska Native (23.1%)	
	C1: placebo							
Takeda (2012)	I1: tadalafil 2.5 mg/d	12 weeks, followed by a 42-week open-label extension phase	> 45 years, IPSS > 13, Qmax 4 to 15 mL/s, prostate volume > 20 cc	"-"	Japan	-	Asian (100%)	-
	I2: tadalafil 5 mg/d							
	C1: placebo							

Table 2. Baseline characteristics (Continued)

Kim (2011)	I1: tadalafil 5 mg/d	12 weeks	Men ≥ 45 years, h/o BPH-LUTS for 6 months or longer, IPSS ≥ 13, Qmax > 5 and < 15 after the washout period	"-"	Korea	-	Asian (100%)	-
	I2: tamsulosin 0.2 mg/d							
	C1: placebo							
Dmochowski (2010)	I1: tamsulosin 20 mg/d	12 weeks	Men > 40 years, longer than 6 months h/o BPH-LUTS; IPSS ≥ 13, with or without BOO	"-"	USA, Canada	-	White (76%)	-
							Black American (12.5%)	
							Hispanic (8%)	
	C1: placebo						Other (3.0%)	
Prost (2011)	I1: tadalafil 5 mg/d	12 weeks	Men > 45 years, BPH-LUTS > 6 months IPSS > 13 and Qmax 4 to 15 mL/s	"-"	Argentina, Germany, Italy, Mexico, USA	-	White (91%)	-
							Black or African American (2.5%)	
							American Indian or Alaska Native (5.2%)	
	C1: placebo						Other (1%)	
Tuncel (2010)	I1: sildenafil 25 mg/4 times weekly + tamsulosin 0.4 mg/d	12 weeks	IPSS > 12, IIEF < 21 (SIHM < 21) treatment-naïve and all participants had ED	-	-	-	-	-
	I2: sildenafil 25 mg/4 times weekly							
	C1: placebo							
Bechara (2008)	I1: tadalafil 20 mg/d + tamsulosin 0.4 mg/d	45 days	Men ≥ 50 years, h/o BPH > 6 months, IPSS ≥ 12, ⁶ PSA ≤ 4 ng/mL, ² Qmax > 5 and < 15 for a minimum voided volume of 125 mL	September 2007 to February 2008	Argentina	-	-	-
	I2: tamsulosin 0.4 mg/d + placebo							

Table 2. Baseline characteristics (Continued)

Roehrborn (2008)	I1: tadalafil 2.5 mg/d	12 weeks	Men > 45 years, BPH-LUTS > 6 months, IPSS > 13, Qmax 4 to 15 mL/s	-	North America, Europe, Australia	-	White (85%)	-
	I2: tadalafil 5 mg/d						Hispanic (11.5%)	
	I3: tadalafil 10 mg/d						Black American (2.42%)	
	I4: tadalafil 20 mg/d						Other (0.5%)	
Stief (2008)	I1: vardenafil 10 mg	12 weeks	Men > 45 to 64 years, BPH-LUTS > 6 months, IPSS > 12	October 2005	Germany	-	White (99%)	-
	C1: placebo			to June 2006			Black Americans (0.5%)	
McVary (2007b)	I1: tadalafil 5 mg/d	12 weeks	Men > 45 years, h/o BPH-LUTS 6 months with IPSS > 13, Qmax > 4 to < 15 mL/s for a voided volume of 125 mL	November 2004	USA	-	White (81%)	-
	C1: placebo			to July 2005			Black American (9.5%)	
							Hispanic (6.5%)	
							Other (2.5%)	
McVary (2007a)	I1: sildenafil 50 to 100 mg/d	12 weeks	Men ≥ 45 years, with IPSS > 12 and IIEF score < 25 All participants had ED	March 2004	USA	-	White (82%)	-
	C1: placebo			to May 2005			Black American (11.5%)	
							Asian (2%)	
							Other (4%)	

- denotes not reported; "-" denotes missing information.

BOO: bladder outflow obstruction; BOOI: Bladder Outflow Obstruction Index; C: comparator; I: intervention; IIEF: International Index of Erectile Function; PSA: prostate-specific antigen; Qmax: maximum urinary flow rate; SD: standard deviation; SHIM: Sexual Health Inventory for Males.

Table 3. Other treatment-related harms - PDEI versus placebo

Name of the subgroup	Number of RCTs	Summary estimate RR (95% CI)
AEs related to vasodilatation	11	1.44 (1.18 to 1.76)
AEs related to body pain	10	3.44 (1.98 to 5.98)
AEs related to GI tract	8	14.19 (5.80 to 34.72)
AEs leading to treatment discontinuation	10	2.20 (1.38 to 3.51)

AE: adverse event; CI: confidence interval; GI: gastrointestinal; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

Table 4. Other treatment-related harms - PDEI versus alpha-blockers

Name of the subgroup	Number of RCTs	Summary estimate RR (95% CI)
AEs related to vasodilatation	3	2.42 (1.05 to 5.56)
AEs related to body pain	3	1.75 (0.38 to 8.18)
AEs related to GI tract	3	4.87 (0.58 to 41.22)
AEs leading to retreatment discontinuation	3	1.26 (0.31 to 5.05)

AE: adverse event; CI: confidence interval; GI: gastrointestinal; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

Table 5. Other treatment-related harms: PDEI + alpha-blockers versus alpha-blockers alone

Name of the subgroup	Number of RCTs	Summary estimate RR (95% CI)
AEs related to vasodilatation	3	4.80 (1.93 to 11.91)
AEs related to GI tract	4	6.00 (0.75 to 48.30)
AEs leading to retreatment discontinuation	3	3.00 (0.13 to 70.53)

AE: adverse event; CI: confidence interval; GI: gastrointestinal; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

Table 6. Other treatment-related harms: PDEI + 5-ARI versus 5-ARI alone

Name of the subgroup	Number of RCTs	Summary estimate RR (95% CI)
AEs related to vasodilatation	1	1.01 (0.46 to 2.22)
AEs related to body pain	1	2.70 (1.07 to 6.81)

Table 6. Other treatment-related harms: PDEI + 5-ARI versus 5-ARI alone *(Continued)*

AEs related to GI tract	1	4.05 (0.87 to 18.92)
AEs leading to retreatment discontinuation	1	0.63 (0.21 to 1.91)
AEs related to sexual function	1	0.51 (0.17 to 1.46)

5-ARI: 5-alpha reductase inhibitor; AE: adverse event; CI: confidence interval; GI: gastrointestinal; PDEI: phosphodiesterase inhibitor; RCT: randomised controlled trial.

APPENDICES

Appendix 1. Search strategy for CENTRAL

#1	[mh "prostatic hyperplasia"]
#2	(Prostat* near (benign* or hyperplasia* or enlargement*))
#3	#1 OR #2
#4	[mh "lower urinary tract symptoms"]
#5	(Lower* next (urinary* or symptom*))
#6	#4 OR #5
#7	[mh "erectile dysfunction"]
#8	(Erect* near (function* or dysfunction* or problem* or issue*))
#9	#7 OR #8
#10	#3 OR #6 OR #9
#11	[mh "phosphodiesterase inhibitors"] OR [mh ^"Sildenafil Citrate"] OR [mh ^tadalafil] OR [mh ^"var-denafil Dihydrochloride"] OR avanafil OR gisadenafil OR mirodenafil OR udenafil
#12	(UK next 92480*) OR (IC next 351*) OR (TA next 1790*) OR (BAY next 38-9456*) OR (DA next 8159*) OR (SK next 3530*) OR (UK next 369003
#13	#11 OR #12
#14	[mh "adrenergic alpha-antagonists"] OR tamsulosin OR alfuzosin OR terazosin OR [mh ^doxazocin] OR silodosin OR naftopidil
#15	[mh "5-alpha reductase inhibitors"] OR [mh ^finasteride] OR [mh ^dutasteride]
#16	#13 OR #14 OR #15
#17	#10 AND #16

Last date of search update - 2 August 2018

Appendix 2. Search strategy for MEDLINE (Ovid®)

#1	Exp Prostatic hyperplasia/ OR "Benign prostatic hyperplasia".tw
#2	BPH.tw
#3	1 OR 2
#4	Exp Lower urinary tract symptoms/ OR " Lower urinary tract symptoms".tw
#5	LUTS.tw
#6	4 OR 5
#7	Erectile dysfunction/ OR "erectile dysfunction".tw OR ED.tw
#8	3 OR 6 OR 7
#9	Exp Phosphodiesterase inhibitors/ OR "Phosphodiesterase inhibitors".tw
#10	Sildenafil/ OR Sildenafil.tw OR UK-92,480.tw
#11	Tadalafil/ OR Tadalafil.tw OR "IC-351".tw
#12	Vardenafil Dihydrochloride/ OR Vardenafil.tw OR "bay-38-9456".tw
#13	Avanafil.tw OR TA-1790.tw
#14	Mirodenafil.tw OR SK-3530.tw
#15	Gisadenafil.tw OR UK-369003.tw
#16	Udenafil.tw OR "DA-8159".tw
#17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
#18	Exp adrenergic alpha-antagonists/ OR "adrenergic alpha-antagonist".tw OR alpha block\$.tw OR "alpha antagonists".tw
#19	Tamsulosin.tw
#20	Alfuzosin.tw
#21	Terazosin.tw
#22	Doxazosin/ OR Doxazosin.tw
#23	Silodosin.tw
#24	Naftopidil.tw
#25	18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
#26	Exp "5-alpha reductase inhibitors"/ OR "5-alpha reductase inhibitor".tw
#27	5ARI.tw

(Continued)

#28	Finasteride/ OR finasteride.tw
#29	Dutasteride/ OR Dutasteride.tw
#30	26 OR 27 OR 28 OR 29
#31	randomized controlled trial.pt
#32	controlled clinical trial.pt
#33	randomized.ab
#34	placebo.ab
#35	Clinical trials as topic.sh
#36	randomly.ab
#37	trial.ti
#38	31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
#39	exp animals/ NOT Humans.sh
#40	38 NOT 39
#41	8 AND (17 OR 25 OR 30) AND 40
#42	8 AND (17 AND 34) AND 40
#43	8 AND (17 AND 25) AND 40
#44	8 AND (17 AND 30) AND 40
#45	8 AND (25 AND 30) AND 40
#46	41 OR 42 OR 43 OR 44 OR 45

Last date of search update 20 February 2018

Appendix 3. Search strategy for Embase® (Elsevier)

#1	'benign prostate hyperplasia'/exp OR 'benign prostate hyperplasia' OR 'prostatic hypertrophy'/exp OR 'prostatic hypertrophy' OR bph
#2	'lower urinary tract symptom'/de OR 'luts'/de OR 'urinary symptoms'
#3	'erectile dysfunction'/exp OR 'erectile dysfunction' OR ed
#4	#1 OR #2 OR #3
#5	'phosphodiesterase inhibitor'/exp

(Continued)

#6	'sildenafil'/exp OR 'tadalafil'/exp OR 'vardenafil'/exp OR 'avanafil'/exp OR 'udenafil'/exp OR 'mirdenafil'/exp OR 'gisadenafil'/exp
#7	#5 OR #6
#8	'alpha adrenergic blocker'/exp OR 'alpha adrenergic antagonist'/exp OR 'adrenergic alpha blocker'
#9	'tamsulosin' OR 'alfuzosin' OR 'terazosin' OR 'doxazosin' OR 'silodosin' OR 'naftopidil' OR 'tamsulosin'/exp OR 'alfuzosin'/exp OR 'terazosin'/exp OR 'doxazosin'/exp OR 'silodosin'/exp OR 'naftopidil'/exp
#10	#8 OR #9
#11	'steroid 5alpha reductase inhibitor'/exp
#12	'finasteride' OR 'dutasteride' OR 'finasteride'/exp OR 'dutasteride'/exp
#13	#11 OR #12
#14	#7 OR #10 OR #13
#15	#4 AND #14
#16	'randomized controlled trial'/exp
#17	'controlled study'/exp
#18	'clinical study'/exp
#19	'clinical trial'/exp
#20	'controlled clinical trial'/exp
#21	'randomization'/exp
#22	'double blind design'/exp OR 'parallel design'/exp OR 'crossover design'/exp
#23	'placebo' OR 'placebo controlled'
#24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 NOT ('nonhuman'/de OR 'animal experiment'/de OR 'in vitro study'/exp OR 'in vivo culture'/de OR 'human experiment'/exp OR 'questionnaire'/exp OR 'intermethod comparison'/de)
#25	#24 AND [humans]/lim
#26	#15 AND #25 AND [male]/lim

Last date of search update - 2 August 2018

Appendix 4. Search strategy for Science Citation Index Expanded (Web of Science™)

#1	TS=("benign prostatic hyperplasia" OR prostat* same (hyper* OR enlarge*) OR BPH)
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(Continued)

#2	TS=(lower* same urinary* same tract symptoms OR LUTS)
#3	TS=(erect* same dysfun* same problem OR ED)
#4	#1 OR #2 OR #3
#5	TS=(phosphodi* same inhibit* same block* OR PDE same inhibit*)
#6	TS=(sildenafil* OR UK-92,480 OR tadalafil* OR IC-351 OR vardenafil* OR BAY-38-9456 OR avanafil* OR TA-1790 OR udenafil* OR DA-8159 OR mirodenafil* OR SK-3530 OR gisadenafil* OR UK-369003)
#7	#5 OR #6
#8	TS=((alpha* same androgen* same antagonist) OR (alpha* same block*) OR (adrenergic* same al-pha* same block*))
#9	TS=(tamsulosin* OR alfuzosin* OR terazosin* OR doxazosin* OR silodosin* OR naftopidil*)
#10	#8 OR #9
#11	TS=((5 alpha* same reductase* same inhibit*) OR 5-ARI OR (5 alpha* same reductase* same block*))
#12	TS=(finasteride* OR dutasteride*)
#13	#11 OR #12
#14	#7 OR #10 OR #13
#15	#14 AND #4
#16	TS=(rando* OR (control* same clinical same trial) OR (clinical same trial) OR (double* same blind*) OR (placebo same control* same trial same study)) or ti=trial
#17	#15 AND #16

Last date of search update - 2 August 2018

Appendix 5. Searches of clinical trials registries

<https://clinicaltrials.gov> (Advanced Search)

("Benign prostatic hyperplasia" OR BPH OR "prostatic hypertrophy" OR LUTS OR "Lower Urinary Tract Symptoms" OR "erectile dysfunction" OR ED) [DISEASE] AND (tadalafil OR sildenafil OR vardenafil OR avanafil OR gisadenafil OR udenafil OR alfuzosin OR terazosin OR silodosin OR naftopidil OR dutasteride OR "phosphodiesterase inhibitor" OR "alpha blocker" OR "5-alpha reductase inhibitor" OR "UK-92480" OR "BAY-38-9456" OR "TA-1790" OR "DA-8159" OR "IC-351" OR "SK-3530") [TREATMENT]

Last date of search update - 13 August 2018

<http://apps.who.int/trialsearch/>

("Benign prostatic hyperplasia" OR BPH OR "prostatic hypertrophy" OR LUTS OR "Lower Urinary Tract Symptoms" OR "erectile dysfunction" OR ED) AND (sildenafil OR vardenafil OR avanafil OR gisadenafil OR udenafil OR alfuzosin OR terazosin OR silodosin

(Continued)

OR naftopidil OR dutasteride OR phosphodiesterase inhibitor OR alpha blocker OR 5-alpha reductase inhibitor OR "UK-92480" OR "BAY-38-9456" OR "TA-1790" OR "DA-8159" OR "IC-351" OR "SK-3530")

Last date of search update - 13 August 2018

WHAT'S NEW

Date	Event	Description
16 November 2018	Amended	Incorrect version of RevMan file was inadvertently published. Re-publishing correct version. Only change is author order and affiliations.

CONTRIBUTIONS OF AUTHORS

Conceiving, designing, co-ordinating, and writing the review: SP, RM.

Developing the search strategy, managing literature searches and search updates: JL.

Undertaking searches: SP, RM, AP.

Screening search results: SP, RM, AP, MMA.

Screening retrieved papers against eligibility criteria: SP, RM, AP, MMA.

Appraising the quality of papers: SP, JLM.

Extracting data from papers: SP, RM, AP, JLM.

Writing to authors of papers for additional information: SP.

Screening data on unpublished studies: MMA, AP.

Managing data for the review and entering data into RevMan: SP, RM.

Analysing data: SP, JLM.

Interpreting data: RM, AP, MMA, SKS, AKM.

Providing a clinical perspective and general advice on the review: RM, AP, MMA, SKS, AKM, ECH.

Reviewing the work for quality and integrity: JLM, SKS, AKM.

DECLARATIONS OF INTEREST

All review authors have no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the conduct of this review, we made the following modifications to make the review more concise and to improve its readability. We made all changes with approval and/or encouragement provided by the Cochrane Urology Editorial Group.

- Objectives: we reorganised primary and secondary objectives into a single primary objective, as per the current standards of Cochrane, and we organised multiple secondary objectives in the order of their importance.
- Methods > Criteria for considering studies for this review > Types of studies: we considered for inclusion in analysis only RCTs in which participants and investigators or outcome assessors were blinded, thereby excluding open-label designs at higher risk for performance and/or detection bias.
- Methods > Criteria for considering studies for this review > Types of Interventions: we did not compare PDEIs versus surgical interventions. Medical therapy for treatment of BPH has become an accepted standard of care since the 1990s. Surgical treatment has dropped dramatically since that time, and the present first line of management is medical therapy for LUTS consistent with BPH. Surgical therapy is usually resorted to only when LUTS symptoms are inadequately relieved with medical therapy, or in cases of complications such as recurrent urinary tract infection or acute urinary retention. Therefore, this comparison was not appropriate and hence was not conducted.
- Methods > Criteria for considering studies for this review > Types of outcome measures: we dropped certain non-patient-important outcomes (IPSS-irritative, IPSS-obstructive, PVR, change in Qmax), as they did not add much value from a clinical point of view.
- Methods> Data collection and analysis > Subgroup analysis: we removed subgroup analyses with low priority to decrease the risk of spurious findings: (i) effect on LUTS when PDEIs were given daily versus on an 'as needed basis'; (ii) effects of PDEIs on LUTS in patients who were previously treated with AB versus treatment-naïve patients; (iii) effects of PDEIs on LUTS in patients with prostate size < 30 cc (cubic centimetres) and > 30 cc; and (iv) effects of PDEIs on LUTS in patients with serum PSA < 2 ng/mL, 2 to 4 ng/mL, and > 4 ng/mL.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Antagonists [therapeutic use]; Drug Therapy, Combination; Lower Urinary Tract Symptoms [*drug therapy] [etiology]; Phosphodiesterase Inhibitors [adverse effects] [*therapeutic use]; Prostatic Hyperplasia [*complications]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Male; Middle Aged