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Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Jung JH, Kim J, MacDonald R, Reddy B, Kim MH, Dahm P

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[Intervention Review]

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

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ABSTRACT

Background

A variety of alpha-blockers are used for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). Silodosin is a novel, more selective alpha-blocker, which is specific to the lower urinary tract and may have fewer side effects than other alpha-blockers.

Objectives

To assess the effects of silodosin for the treatment of LUTS in men with BPH.

Search methods

We performed a comprehensive search using multiple databases (Cochrane Library, MEDLINE, EMBASE, Scopus, Google Scholar, and Web of Science), trials registries, other sources of grey literature, and conference proceedings with no restrictions on the language of publication or publication status up until 13 June 2017.

Selection criteria

We included all parallel, randomized controlled trials. We also included cross-over designs.

Data collection and analysis

Two review authors independently classified studies and abstracted data from the included studies. We performed statistical analyses using a random-effects model and interpreted them according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We rated the quality of evidence according to the GRADE approach.

Main results

We included 19 unique studies with 4295 randomized participants across four comparisons for short-term follow-up. The mean age, prostate volume, and International Prostate Symptom Score were 66.5 years, 38.2 mL, and 19.1, respectively.

Silodosin versus placebo

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

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Based on four studies with a total of 1968 randomized participants, silodosin may reduce urologic symptom scores in an appreciable number of men (mean difference (MD) -2.65, 95% confidence interval (CI) -3.23 to -2.08; low-quality evidence). Silodosin likely does not result in a clinically important reduction in quality of life (MD -0.42, 95% CI -0.71 to -0.13; moderate-quality evidence). It may not increase rates of treatment withdrawal for any reason (relative risk (RR) 1.08, 95% CI 0.70 to 1.66; low-quality evidence). We are uncertain about the effect of silodosin on cardiovascular adverse events (RR 1.28, 95% CI 0.67 to 2.45; very low-quality evidence). Silodosin likely increases sexual adverse events (RR 26.07, 95% CI 12.36 to 54.97; moderate-quality evidence); this would result in 180 more sexual adverse events per 1000 men (95% CI 82 more to 388 more).

Silodosin versus tamsulosin

Based on 13 studies with a total of 2129 randomized participants, silodosin may result in little to no difference in urologic symptom scores (MD -0.04, 95% CI -1.31 to 1.24; low-quality evidence) and quality of life (MD -0.15, 95% CI -0.53 to 0.22; low-quality evidence). We are uncertain about treatment withdrawals for any reason (RR 1.02, 95% CI 0.62 to 1.69; very low-quality evidence). Silodosin may result in little to no difference in cardiovascular adverse events (RR 0.77, 95% CI 0.53 to 1.12; low-quality evidence). Silodosin likely increases sexual adverse events (RR 6.05, 95% CI 3.55 to 10.31; moderate-quality evidence); this would result in 141 more sexual adverse events per 1000 men (95% CI 71 more to 261 more).

Silodosin versus naftopidil

Based on five studies with a total of 763 randomized participants, silodosin may result in little to no differences in urologic symptom scores (MD -0.85, 95% CI -2.57 to 0.87; low-quality evidence), quality of life (MD -0.17, 95% CI -0.60 to 0.27; low-quality evidence), treatment withdrawal for any reason (RR 1.25, 95% CI 0.81 to 1.93; low-quality evidence), and cardiovascular adverse events (RR 1.02, 95% CI 0.41 to 2.56; low-quality evidence). Silodosin likely increases sexual adverse events (RR 5.93, 95% CI 2.16 to 16.29; moderate-quality evidence); this would result in 74 more sexual adverse events per 1000 men (95% CI 17 more to 231 more).

Silodosin versus alfuzosin

Based on two studies with a total of 155 randomized participants, silodosin may or may not result in a clinically important increase in urologic symptom scores (MD 3.83, 95% CI 0.12 to 7.54; low-quality evidence). Silodosin likely results in little to no difference in quality of life (MD 0.14, 95% CI -0.46 to 0.74; moderate-quality evidence). We found no event of treatment withdrawal for any reason. Silodosin may not reduce cardiovascular adverse events (RR 0.67, 95% CI 0.36 to 1.24; low-quality evidence) but likely increases sexual adverse events (RR 37.21, 95% CI 5.32 to 260.07; moderate-quality evidence); this would result in 217 more sexual adverse events per 1000 men (95% CI 26 more to 1000 more).

Authors' conclusions

Silodosin may reduce urologic symptom scores in an appreciable number of men compared to placebo. Quality of life and treatment withdrawals for any reason appears similar. Its efficacy appears similar to that of other alpha blockers (tamsulosin, naftopidil and alfuzosin) but the rate of sexual side effects is likely higher. Our certainty in the estimates of effect was lowered due to study limitations, inconsistency and imprecision.

PLAIN LANGUAGE SUMMARY

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Review question

Does silodosin improve bothersome urinary symptoms in men with an enlarged prostate?

Background

Prostate enlargement is common in men as they get older and may cause difficulties in urination such as a weak stream, having to get up at night and a feeling of not emptying the bladder completely. Silodosin is a newer medication that may help with these symptoms and may cause fewer unwanted drug effects. We did this review to compare silodosin to placebo (dummy drug) and other medications.

Study characteristics

We included 19 studies with 4295 men. Participants' average age was 66.5 years. All studies included men aged over 40 years and reported that on average these men had a moderate degree of bothersome urinary symptoms.

Key results

Silodosin may improve urinary symptoms compared to placebo. It may have comparable effects on urinary symptoms, quality of life, treatment discontinuation for any reason, and unwanted drug effects compared to other medications. However, silodosin likely increases unwanted sexual side effects compared to placebo and other medications.

Quality of the evidence

The quality of evidence for most outcomes was low. This means that the true effect may be substantially different from what this review shows.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Silodosin compared to placebo for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Silodosin compared to placebo for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia

Setting: likely outpatients

Intervention: silodosin

Comparator: placebo

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with silodosin
Urologic symptom scores Assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 3 months	1743 (3 RCTs)	⊕⊕⊕⊖ Low a,b	-	The mean change of urologic symptom scores ranged from -5.30 to -3.50	MD 2.65 lower (3.23 lower to 2.08 lower)
QoL Assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: mean 3 months	820 (2 RCTs)	⊕⊕⊕⊖ Moderate a,c	-	The mean change of QoL ranged from -1.10 to -0.80	MD 0.42 lower (0.71 lower to 0.13 lower)
Treatment withdrawal due to any reason Follow-up: mean 3 months	1703 (3 RCTs)	⊕⊕⊕⊖ Low a,b	RR 1.08 (0.70 to 1.66)	Study population	
				83 per 1000	7 more per 1000 (25 fewer to 55 more)
Cardiovascular adverse events Follow-up: mean 3 months	1967 (4 RCTs)	⊕⊕⊕⊖ Very low a,b,d	RR 1.28 (0.67 to 2.45)	Study population	
				42 per 1000	12 more per 1000 (14 fewer to 61 more)
				Assumed baseline risk ^e	
				61 per 1000	17 more per 1000

					(20 fewer to 88 more)
Sexual adverse events Follow-up: mean 3 months	1967 (4 RCTs)	⊕⊕⊕⊖ Moderate ^a	RR 26.07 (12.36 to 54.97)	Study population	
				7 per 1000	180 more per 1000 (82 more to 388 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).

CI: confidence interval; **IPSS:** International Prostate Symptom Score; **MD:** mean difference; **QoL:** quality of life; **RCTs:** randomized controlled trials; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

^aDowngraded by one level for study limitations: unclear or high risk of bias for one or more domains among the included studies.

^bDowngraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

^cNot downgraded for inconsistency despite moderate heterogeneity given that likely not clinically meaningful.

^dDowngraded by one level for inconsistency: substantial heterogeneity among the included studies.

^eEstimates for control event rates for cardiovascular adverse events come from [Rosenzweig 1993](#).

Summary of findings 2. Silodosin compared to tamsulosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Silodosin compared to tamsulosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia

Setting: likely outpatients

Intervention: silodosin

Comparator: tamsulosin

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with tamsulosin	Risk difference with silodosin

Urologic symptom scores Assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: range 4 weeks to 12 months	1708 (10 RCTs)	⊕⊕⊕⊕ Low a,b	-	The mean change of urologic symptom scores ranged from -15.60 to -4.60	MD 0.04 lower (1.31 lower to 1.24 higher)
QoL Assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: range 4 weeks to 12 months	1707 (10 RCTs)	⊕⊕⊕⊕ Low a,b	-	The mean change of QoL ranged from -3.60 to -0.90	MD 0.15 lower (0.53 lower to 0.22 higher)
Treatment withdrawal due to any reason Follow-up: range 4 weeks to 12 months	1573 (10 RCTs)	⊕⊕⊕⊕ Very low a,b,c	RR 1.02 (0.62 to 1.69)	Study population 121 per 1000	2 fewer per 1000 (46 fewer to 84 more)
Cardiovascular adverse events Follow-up: range 4 weeks to 3 months	1955 (11 RCTs)	⊕⊕⊕⊕ Low a,c	RR 0.77 (0.53 to 1.12)	Study population 63 per 1000	14 fewer per 1000 (29 fewer to 8 more)
Sexual adverse events Follow-up: range 4 weeks to 3 months	1849 (10 RCTs)	⊕⊕⊕⊕ Moderate ^a	RR 6.05 (3.55 to 10.31)	Study population 28 per 1000	141 more per 1000 (71 more to 261 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).

CI: confidence interval; **IPSS:** International Prostate Symptom Score; **MD:** mean difference; **QoL:** quality of life; **RCTs:** randomized controlled trials; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

^aDowngraded by one level for study limitations: unclear or high risk of bias for one or more domains among the included studies.

^bDowngraded by one level for inconsistency: considerable heterogeneity among the included studies.

^cDowngraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

Summary of findings 3. Silodosin compared to naftopidil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Silodosin compared to naftopidil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia

Setting: likely outpatients

Intervention: silodosin

Comparator: naftopidil

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with naftopidil	Risk difference with silodosin
Urologic symptom scores Assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: range 6 weeks to 3 months	652 (5 RCTs)	⊕⊕⊕⊕ Low a,b	-	The mean change of urologic symptom scores ranged from -7.52 to -3.56	MD 0.85 lower (2.57 lower to 0.87 higher)
QoL Assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: range 6 weeks to 3 months	652 (5 RCTs)	⊕⊕⊕⊕ Low a,b	-	The mean change of QoL ranged from -1.60 to -0.95	MD 0.17 lower (0.6 lower to 0.27 higher)
Treatment withdrawal due to any reason Follow-up: range 2 months to 3 months	659 (4 RCTs)	⊕⊕⊕⊕ Low a,c	RR 1.25 (0.81 to 1.93)	Study population 102 per 1000	25 more per 1000 (19 fewer to 94 more)
Cardiovascular adverse events Follow-up: range 6 weeks to 3 months	808 (5 RCTs)	⊕⊕⊕⊕ Low a,c	RR 1.02 (0.41 to 2.56)	Study population 23 per 1000	0 more per 1000 (13 fewer to 35 more)
Sexual adverse events Follow-up: range 6 weeks to 3 months	405 (4 RCTs)	⊕⊕⊕⊕ Moderate a	RR 5.93 (2.16 to 16.29)	Study population 15 per 1000	74 more per 1000 (17 more to 231 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).

CI: confidence interval; **IPSS:** International Prostate Symptom Score; **MD:** mean difference; **QoL:** quality of life; **RCTs:** randomized controlled trials; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

^aDowngraded by one level for study limitations: unclear or high risk of bias for one or more domains among the included studies.

^bDowngraded by one level for inconsistency: considerable heterogeneity among the included studies.

^cDowngraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

Summary of findings 4. Silodosin compared to alfuzosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Silodosin compared to alfuzosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia

Setting: likely outpatients

Intervention: silodosin

Comparator: alfuzosin

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with alfuzosin	Risk difference with silodosin
Urologic symptom scores Assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 3 months	60 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	-	The mean change of urologic symptom scores was -16.93	MD 3.83 higher (0.12 higher to 7.54 higher)
QoL Assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible)	60 (1 RCT)	⊕⊕⊕⊖ Moderate ^a	-	The mean change of QoL was -4.27	MD 0.14 higher (0.46 lower to 0.74 higher)

Follow-up: mean 3 months				
Treatment withdrawal due to any reason Follow-up: mean 3 months	60 (1 RCT)	⊕⊕⊕⊖ Low ^{a,c}	Not estimable	Study population - -
Cardiovascular adverse events Follow-up: mean 3 months	60 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	RR 0.67 (0.36 to 1.24)	Study population 500 per 1000 165 fewer per 1000 (320 fewer to 120 more) Assumed baseline risk ^d 44 per 1000 15 fewer per 1000 (11 fewer to 28 more)
Sexual adverse events Follow-up: mean 3 months	95 (1 RCT)	⊕⊕⊕⊖ Moderate ^a	RR 37.21 (5.32 to 260.07)	Study population 21 per 1000 770 more per 1000 (92 more to 5,512 more) Assumed baseline risk ^d 6 per 1000 217 more per 1000 (26 more to 1000 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).

CI: confidence interval; IPSS: International Prostate Symptom Score; MD: mean difference; QoL: quality of life; RCTs: randomized controlled trials; RR: risk ratio

GRADE Working Group grades of evidence

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

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

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

^aDowngraded by one level for study limitations: unclear or high risk of bias for one or more domains in the included study.

^bDowngraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

^cDowngraded by one level for imprecision: no event (very rare event).

^dEstimates for control event rates for cardiovascular and sexual adverse events come from [Van Kerrebroec 2002](#).

BACKGROUND

Description of the condition

Benign prostatic hyperplasia (BPH) is characterized by an unregulated proliferative process of connective tissue, smooth muscle and glandular epithelium within the prostate, and is one of the most common conditions in elderly men (Roehrborn 2008). The prevalence of BPH rises significantly with increased age. Autopsy studies have observed a histological prevalence of 40% and 70% in the sixth and eighth decades of life, respectively (Barry 1997; Egan 2016; Roehrborn 2008). BPH can lead to troublesome lower urinary tract symptoms (LUTS), including storage disturbances (such as daytime urinary urgency and nocturia) or voiding disturbances (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding), or both (AUA Practice Guidelines Committee 2003; EAU 2017; McVary 2011). LUTS secondary to BPH (LUTS/BPH) may negatively impact on public health and reduce quality of life because BPH can progress over time and cause serious consequences, such as acute urinary retention (AUR), urinary tract infection, and upper urinary tract deterioration (Crawford 2006; Kozminski 2015; Martin 2014). In 2000, the direct treatment cost for LUTS/BPH in the USA was more than USD 1 billion. Based on the Hospital Episode Statistics data from the UK, LUTS/BPH is the fifth most expensive disease and costs GBP 1.16 billion each year (Cornu 2010).

Diagnosis

Initial assessment of LUTS/BPH includes patient history, review of current medications, physical exam including a digital rectal examination, urinalysis, a frequency/volume chart, and validated symptom questionnaires such as the International Prostate Symptom Score (IPSS) and BPH Impact Index (BII) (EAU 2017; Juliao 2012; McVary 2011). The IPSS questionnaire is composed of three domains related to storage symptoms (frequency, urgency, and nocturia); four domains related to voiding symptoms (hesitancy, weak stream, intermittence, and incomplete emptying); and one quality of life domain (AUA Practice Guidelines Committee 2003; Barry 1992). Seven symptom domains use a six-point scale ranging from 0 (none) to 5 (5 or more) (Barry 1992). The quality of life domain is assigned a score from 1 to 6 (ordinal and range from 0 to 6: 0 = delighted, 1 = pleased, 2 = mostly satisfied, 3 = mixed, 4 = mostly dissatisfied, 5 = unhappy, 6 = terrible) (AUA Practice Guidelines Committee 2003; Barry 1992).

Simultaneous with the development of the IPSS, the BII was developed to assess the effect of LUTS/BPH on the men's health. The BII questionnaire is composed of four items: physical discomfort (0 = none, 1 = only a little, 2 = some, 3 = a lot); worry item (0 = none, 1 = only a little, 2 = some, 3 = a lot); bother item (0 = not at all bothersome, 1 = bothers me a little, 2 = bothers me some, 3 = bothers me a lot); the interference with usual activities item (0 = none of the time, 1 = a little of the time, 2 = some of the time, 3 = most of the time, 4 = all of the time) (Barry 1995). In addition, measurement of the maximum flow rate (Q_{max}) and postvoid residual (PVR) are widely used, noninvasive tests to evaluate joint functioning between bladder and prostate (EAU 2017; McVary 2011). Although diagnostic thresholds of Q_{max} and PVR have not been determined, low Q_{max} and large PVR have been associated with an increased risk of symptom deterioration (Crawford 2006; Kozminski 2015). Other optional tests include imaging of the urinary tract and prostate, urodynamic evaluation

of bladder function, and cystoscopy to predict the response to medical therapy or determine the need for invasive therapy and therefore, the best approach (EAU 2017; McVary 2011).

Treatment

Treatment decisions are based on symptoms and degree of bother (EAU 2017; McVary 2011). Watchful waiting is a reasonable treatment strategy for men with mild LUTS (IPSS: 0 to 7) or those who do not perceive their symptoms to be particularly bothersome (Netto 1999). Lifestyle interventions such as modifying fluid intake or toileting behavior can be used as conservative treatments in men with mild LUTS (Yap 2009). In men with bothersome, moderate (IPSS: 8 to 19) to severe LUTS (IPSS: 20 to 35), surgical and medical therapies are the treatment options, and the choice of treatment depends on a number of factors such as the severity of disease, risk of progression, patient preference, and morbidity (EAU 2017; McVary 2011).

Recently, the dynamic component of BPH has been elucidated, with a focus on symptoms rather than prostate enlargement, which has led to a shift from surgery to medical treatment (Yoo 2012). Alpha-adrenergic receptor blockers (ABs), which reduce smooth-muscle tone in the prostate and bladder neck with/without 5-alpha reductase inhibitors (5-ARIs), which reduce prostate volume by inducing epithelial atrophy, are an established treatment in LUTS/BPH and have been widely used as first-line therapy for decades (McConnell 2003; Milani 2005; Yoo 2012). In particular, ABs that can decrease smooth muscle tone in the prostate and bladder neck have been considered as fundamental pharmacotherapy for men with BPH (Cornu 2010; Milani 2005; Yoo 2012). Prior systematic reviews have shown that ABs can typically reduce the IPSS by 20% to 50% and increase the Q_{max} by 15% to 45% (MacDonald 2005; Wilt 2006). ABs are the most commonly prescribed category of drug, accounting for about 70% of all medications prescribed in 2008 (Cornu 2010). Adverse effects of ABs include postural hypotension, dizziness, headache, asthenia, syncope, peripheral edema, and retrograde ejaculation, which cause approximately 4% to 10% of men to withdraw from AB treatment (Djavan 1999; Gacci 2014; MacDonald 2005; Schulman 2003; Wilt 2006).

Other medical therapies, such as anticholinergics and desmopressin, have been used with ABs, depending on the main symptoms of patients (Brasure 2016; Dahm 2016; EAU 2017). Alternatively, a phosphodiesterase type 5 inhibitor, tadalafil (5 mg once daily), has been licensed for the treatment of male LUTS in the last few years, and various plant extracts have been proposed for the treatment of male LUTS (EAU 2017; Keehn 2016; Oelke 2012). In men with LUTS/BPH refractory to conservative/medical treatment or in cases of absolute clinical indications (e.g. AUR, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal insufficiency), surgical techniques should be considered (EAU 2017; McVary 2011). Transurethral resection of the prostate (TURP) is regarded as the standard surgical procedure for the treatment of LUTS/BPH (EAU 2017; Juliao 2012; McVary 2011). Recently, minimal invasive laser therapies such as holmium laser enucleation of the prostate and photoselective vaporization were introduced as treatment alternatives to TURP (Nair 2016).

Description of the intervention

Silodosin is a new subtype selective AB that was approved in Japan in 2006, and more recently has received approval in the USA

and Europe (Kawabe 2006a; Yoshida 2007). An initial randomized, placebo-controlled trial, which was conducted in Japan showed a greater reduction in IPSS after 12 weeks' treatment compared to both tamsulosin – which is a well established AB for LUTS – and placebo. Furthermore, a clinical benefit in IPSS in the silodosin group over placebo was found from one week onwards (Kawabe 2006a). There were no significant differences in the incidence of cardiovascular adverse events between the silodosin and tamsulosin groups. Abnormal ejaculation was more frequent in the silodosin group than in the tamsulosin group (22.3% versus 1.6%), but only five men (2.9%) discontinued treatment due to abnormal ejaculation (Kawabe 2006a).

How the intervention might work

The A1a adrenergic receptors are a class of G protein-coupled receptors that consists of three homologous subtypes, including A1a, A1b, and A1d receptors. The A1a receptor subtype predominates in the human prostate, bladder neck, and urethra (Minneman 1994; Schilit 2009). On the other hand, A1b receptor subtypes are mainly expressed in the peripheral vasculature and are important in the regulation of blood pressure. A1d receptor is expressed in the detrusor muscle of the bladder and the sacral region of the spinal cord (Minneman 1994; Schilit 2009). In the initial in vitro study, it was shown that silodosin had a high binding ratio (162:1) for A1a versus A1b receptors, which can be more specific to the lower urinary tract, and may therefore induce a therapeutic effect without cardiovascular side effects, such as dizziness, headache, and orthostatic hypotension related to vasodilation, compared with the other ABs, which have either no specific selectivity for the different adrenergic receptor subtypes (alfuzosin, doxazosin, terazosin) or a limited selectivity for the A1a receptor (tamsulosin) (Osman 2012; Schilit 2009; Yoshida 2007).

Why it is important to do this review

It is unclear whether the high affinity of silodosin to A1a adrenergic receptor actually translates into more clinical benefits and fewer adverse effects in clinical practice (Cui 2012; Novara 2013). While there are existing systematic reviews that compare silodosin to other agents used to treat men with LUTS/BPH, none so far has used the same rigorous methodology as Cochrane Reviews, which include the GRADE approach (Cui 2012; Fusco 2016; Novara 2013). In this era, with the availability of numerous ABs to treat LUTS/BPH, the findings of this Cochrane Review will be relevant to policymakers, healthcare providers and patients.

OBJECTIVES

To assess the effects of silodosin for the treatment of LUTS in men with BPH.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel, randomized controlled trials regardless of their publication status or language of publication. We also included cross-over designs.

Types of participants

We included adult men (aged 40 years and over) with LUTS/BPH. The age limitation was based on the observation that the prevalence of BPH increases in middle-aged and older men (Barry 1997; Egan 2016), and is infrequent in younger men.

We excluded trials of men with a known neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease, and men who have been treated with surgery for BPH already. We included studies in which only a subset of participants were relevant to this review.

Types of interventions

We planned to investigate the following comparisons of experimental intervention versus comparator intervention. Concomitant interventions had to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- Silodosin
- Silodosin + any 5-ARIs (if available)

Silodosin at 8 mg/day is the clinically recommended dosage in Japan, Europe, and the USA (Chapple 2011; Kawabe 2006a; Marks 2009). A recent study reported that silodosin at 4 mg/day was also useful for Japanese men with BPH, in order to improve treatment compliance (Seki 2015). We included trials with a dosage of silodosin at 8 mg/day (4 mg twice daily or 8 mg once daily) and 4 mg/day.

Comparator interventions

- Placebo
- Other ABs
- Other ABs + any 5-ARIs (if available)

Comparisons

- Silodosin versus placebo
- Silodosin versus other ABs
- Silodosin + any 5-ARIs versus other ABs + any 5-ARIs (if available)

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urologic symptom scores
- Quality of life
- Treatment withdrawals for any reason

Secondary outcomes

- Treatment withdrawals due to adverse events
- AUR
- Surgical intervention for LUTS/BPH
- Cardiovascular adverse events
- Sexual adverse events

Method and timing of outcome measurement

- Urologic symptom scores: final value or change from baseline assessed with a validated scale (such as IPSS)
- Quality of life: final value or change from baseline assessed with a validated scale (such as IPSS-quality of life or BII scores)
- Treatment withdrawals for any reason: defined as treatment discontinuation from any cause at any time after participants were randomized to intervention/comparator groups
- Treatment withdrawals due to adverse events: defined as treatment discontinuation from adverse event at any time after participants were randomized to intervention/comparator groups
- AUR: events requiring catheterization after intervention
- Surgical intervention for LUTS/BPH: events requiring other surgical treatment modalities (e.g. TURP) after intervention
- Cardiovascular adverse events: such as dizziness, headache, orthostatic hypotension, and syncope
- Sexual adverse events: such as retrograde ejaculation, anejaculation, and decreased libido

We used the clinically important difference for the review outcomes to rate the quality of the evidence in the 'Summary of findings' tables (Jaeschke 1989; Johnston 2013). When the mean difference (MD) or risk ratio (RR) is equal to or larger than the minimal clinically important difference (MCID), we would assume that many participants may have gained a clinically meaningful improvement from treatment; when the MD is at least half of the MCID but less than the MCID, an appreciable number of participants have likely achieved a clinically meaningful improvement; and when the MD is less than one-half of the MCID, it is unlikely that an appreciable number of participants have achieved a clinically meaningful improvement (Johnston 2010). We considered MCID in the IPSS and BII score to be 3 and 0.5 points, respectively (Barry 1995). We did not find any published information on a MCID for the IPSS-quality of life question. We used a MCID of 1 to assess efficacy and comparative effectiveness (Brasure 2016). We did not establish thresholds for treatment withdrawals due to adverse events, AUR, surgical intervention for LUTS/BPH, cardiovascular adverse events, and sexual adverse events. We considered the clinically important differences of all listed outcomes above as a relative risk increase of at least 25% (Guyatt 2011a).

We considered outcomes measured up to and including 12 months after randomization as short term, and later than 12 months as long term.

- Up to 12 months (short term)
- More than 12 months (long term)

Main outcomes for 'Summary of findings' tables

We present 'Summary of findings' tables, reporting the following outcomes listed according to priority.

- Urologic symptom scores
- Quality of life
- Treatment withdrawals for any reason
- Cardiovascular adverse events
- Sexual adverse events

Search methods for identification of studies

We performed a comprehensive search with no restrictions on the language of publication or publication status. We updated searches within three months prior to the anticipated publication of the review.

Electronic searches

We initially searched the following sources from inception of each database to 1 September 2016. The date of last search of all databases was 13 June 2017. See Appendix 1.

- Cochrane Library (via Wiley)
 - * *Cochrane Database of Systematic Reviews*
 - * Cochrane Central Register of Controlled Trials (CENTRAL)
 - * Database of Abstracts of Reviews of Effects
 - * Health Technology Assessment Database
- MEDLINE (via Pubmed)
- EMBASE (via Ovid)
- Scopus
- Google Scholar
- Web of Science

We also searched the following trials registers on 1 September 2016 and again on 13 June 2017.

- ClinicalTrials.gov (clinicaltrials.gov/)
- World Health Organization International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/)
- Grey Literature Report (www.greylit.org/)

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We also contacted study authors of included trials to identify any further studies that we might have missed. We contacted drug/device manufacturers for ongoing or unpublished trials. We searched for unpublished studies by handsearching the abstract proceedings of the annual meetings of the American Urological Association, European Association of Urology, and International Continence Society for the last three years (2014 to 2016) and then updated the search for the most recent year (2017).

Data collection and analysis

Selection of studies

We used reference management software to identify and remove potential duplicate records (EndNote). Two review authors (JHJ, JK) independently scanned the abstract, title, or both, of remaining records retrieved, to determine which studies should be assessed further. Two review authors (JHJ, JK) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We used Covidence for title/abstract, and full-text screening. We resolved any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement was not possible, we

planned to designate the study as 'awaiting classification' and contact study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in a [Characteristics of excluded studies](#) table. We present an adapted PRISMA flow diagram showing the process of study selection ([Liberati 2009](#)).

Data extraction and management

We developed a dedicated data abstraction form that we pilot tested ahead of time.

For studies that fulfilled the inclusion criteria, two review authors (JHJ, JK) independently abstracted the following information, which we provided in the [Characteristics of included studies](#) table.

- Study design
- Study dates
- Study settings and country
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS)
- Participant details, baseline demographics (e.g. age, ethnic background, IPSS)
- The number of participants by study and by study arm
- Details of relevant experimental and comparator interventions such as such as frequency (e.g. once a day or twice a day) and treatment duration (in weeks or months)
- Definitions of relevant outcomes, and method (e.g. type of instrument such as IPSS) and timing of outcome measurement (e.g. in weeks or months) as well as any relevant subgroups (e.g. based on age)
- Study funding sources
- Declarations of interest by primary investigators

We extracted outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we obtained numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we obtained means and standard deviations or data necessary to calculate this information.

We resolved any disagreements by discussion, or, if required, by consultation with a third review author (PD).

We provided information (including trial identifier), about potentially relevant, ongoing studies in the table [Characteristics of ongoing studies](#).

We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximized yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data-set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (JHJ, JK) assessed the risk of bias of each included study independently. We resolved disagreements by consensus, or by consultation with a third review author (PD).

We assessed risk of bias using Cochrane's 'Risk of bias' assessment tool ([Higgins 2011b](#)) for the following domains.

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

We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We presented a 'Risk of bias' summary figure to illustrate these findings.

For selection bias (random sequence generation and allocation concealment), we evaluated risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we considered that all outcomes were susceptible to performance bias and assessed in one group.

For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.

We defined the following outcomes as subjective outcomes:

- Urologic symptom scores
- Quality of life
- Treatment withdrawals for any reason
- Treatment withdrawals due to adverse events
- Cardiovascular adverse events
- Sexual adverse events

We defined the following outcomes as objective outcomes:

- AUR
- Surgical intervention for LUTS/BPH

We initially assessed attrition bias (incomplete outcome data) on a per-outcome basis but created groups of outcomes based on similar reporting characteristic.

For reporting bias (selective reporting), we evaluated risk of bias on a trial level.

We further summarized the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)).

Measures of treatment effect

We expressed dichotomous data as RRs with 95% confidence intervals (CIs). We expressed continuous data as MDs with 95% CIs unless different studies used different measures to assess the same outcome, in which case we expressed data as standardized MDs with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. For cross-over trials or trials with more than two intervention groups, we planned to incorporate these study designs in meta-analysis in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c)

Dealing with missing data

We obtained missing data from study authors and performed intention-to-treat analyses if data were available; we otherwise performed available case analyses. We investigated attrition rates, for example, dropouts, losses to follow-up and withdrawals, and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity in the meta-analysis (Higgins 2002; Higgins 2003); we interpreted the I^2 statistic as follows (Deeks 2011).

- 0% to 40%: may not be important
- 30% to 60%: may indicate moderate heterogeneity
- 50% to 90%: may indicate substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

If we included 10 studies or more investigating a particular outcome, we planned to use funnel plots to assess small study effects (Sterne 2011). Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We therefore interpreted results carefully. However, there were fewer than 10 studies for each comparison.

Data synthesis

We summarized data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance

method. We used Review Manager 5 software to perform analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out subgroup analyses with investigation of interactions.

- Severity of baseline symptoms based on IPSS (0 to 7 = mildly symptomatic; 8 to 19 = moderately symptomatic; 20 to 35 = severely symptomatic)
- Participant age (less than 65 years versus 65 years and older)

These subgroup analyses are based on the following observations.

- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by the baseline scores (Barry 1995).
- Tolerability of other ABs (as the main comparator) may differ by patient age but that this may be less the case for silodosin, which would represent a potential benefit of this agent (Kozminski 2015; Lepor 2007; Schilit 2009).

We planned to perform subgroup analyses limited to the primary outcomes.

Sensitivity analysis

We planned to perform sensitivity analyses limited to the primary outcomes in order to explore the influence of the following factors (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk' of bias

'Summary of findings' tables

We presented the quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (JHJ, JK, or RM) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT 2015. We resolved any discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). For each comparison, we presented a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the 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 the overall confidence in effect estimates for each outcome (Guyatt 2011b; Schünemann 2011).

RESULTS

Description of studies

Results of the search

We identified 645 records through electronic database searching, including 52 records in trials registers. We found no records in the grey literature repository nor through handsearching abstract

proceedings of relevant meetings from the last three years. We identified further six records through other sources by searching the reference lists of reviews ([Alcántara Montero 2016](#); [Brasure 2016](#)) and one additional protocol for [Takeshita 2016](#). After removal of duplicates, we screened the titles and abstracts of 458 records, and excluded 378 records. We screened 80 full-text articles, and

excluded 23 studies (24 records) that did not meet the inclusion criteria or were not relevant to the question under trial. Two studies are ongoing and 12 studies are awaiting classification. We included a total of 19 studies (42 records) in the review. The flow of literature through the assessment process is shown in the PRISMA flowchart ([Figure 1](#)).

Figure 1. Flow diagram

Figure 1. (Continued)

meta-analysis (n = 19 studies (42 records))

Included studies

Details of included studies are presented elsewhere (see [Characteristics of included studies](#); [Table 1](#); [Table 2](#)).

Source of data

We included 16 published studies, two abstract proceedings ([Jung 2012](#); [Yamanishi 2011](#)), and one record ([NCT00793819](#)) from a trials register. Of 16 published studies, we found two studies ([Pande 2014](#); [Yokoyama 2011](#)) by searching the reference lists of an existing review ([Brasure 2016](#)) and the remaining studies were identified through our electronic database search. Eighteen studies were published in English and one was published in Japanese ([Masuda 2012](#)), which was translated into English using Google translator. We attempted to contact all corresponding authors of included trials to obtain additional information on study methodology and results, and received replies from nine ([Chapple 2011](#); [Jung 2012](#); [Masuda 2012](#); [Pande 2014](#); [Takeshita 2016](#); [Yamaguchi 2013](#); [Yamanishi 2011](#); [Yokoyama 2011](#); [Yokoyama 2012](#); see [Appendix 2](#)).

Study design and settings

We included 14 parallel, randomized controlled trials ([Chapple 2011](#); [Jung 2012](#); [Kawabe 2006a](#); [Manjunatha 2016a](#); [Marks 2009](#); [Matsukawa 2016](#); [Natarajan 2015](#); [NCT00793819](#); [Pande 2014](#); [Shirakawa 2013](#); [Yamaguchi 2013](#); [Yamanishi 2011](#); [Yokoyama 2011](#); [Yu 2011](#)) and five cross-over trials ([Masuda 2012](#); [Miyakita 2010](#); [Takeshita 2016](#); [Watanabe 2011](#); [Yokoyama 2012](#)). Five of 19 studies were reported as 'double-blinded'. The participants and investigators were blinded in three studies ([Marks 2009](#); [NCT00793819](#); [Yu 2011](#)) and participants and personnel were blinded in one study ([Chapple 2011](#)). One study was reported to be 'double-blinded' but it was not clear who was blinded ([Kawabe 2006a](#)). Four studies were open-label trials ([Jung 2012](#); [Manjunatha 2016a](#); [Matsukawa 2016](#); [Shirakawa 2013](#)). The remaining five trials had no information regarding blinding. There were three trials with run-in periods ([Chapple 2011](#); [Marks 2009](#); [Yu 2011](#)).

All studies were likely conducted in an outpatient clinic setting. Three studies explicitly stated that the trial was conducted in an outpatient clinic setting ([Kawabe 2006a](#); [Matsukawa 2016](#); [Pande 2014](#)). Most of the included studies ([Jung 2012](#); [Kawabe 2006a](#); [Manjunatha 2016a](#); [Masuda 2012](#); [Matsukawa 2016](#); [Miyakita 2010](#); [Natarajan 2015](#); [Pande 2014](#); [Shirakawa 2013](#); [Takeshita 2016](#); [Watanabe 2011](#); [Yamaguchi 2013](#); [Yokoyama 2011](#); [Yokoyama 2012](#); [Yu 2011](#)) were performed in Asia, except two studies, which were performed in Europe ([Chapple 2011](#)) and the USA ([Marks 2009](#)). Eight trials ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#); [Masuda 2012](#); [Matsukawa 2016](#); [Miyakita 2010](#); [Takeshita 2016](#); [Watanabe 2011](#)) were multicenter trials. The studies were performed from 2005 to 2015.

Participants

We included a total of 4295 randomized participants (silodosin 1955, placebo 834, tamsulosin 1049, naftopidil 380, alfuzosin 77), of which a total of 3751 finished the trials (silodosin 1684, placebo 769, tamsulosin 888, naftopidil 333, alfuzosin 77). However, two

studies ([Natarajan 2015](#); [Yamanishi 2011](#)), that compared silodosin to tamsulosin, did not report the number of participants who completed the trial in each group. All studies included men aged over 40 years. The mean age, prostate volume, prostate specific antigen (PSA), International Prostate Symptom Score (IPSS), and maximum flow rate (Qmax) of the participants were 66.5 years, 38.2 mL, 3.14 ng/mL, 19.1, and 9.5 mL/s, respectively.

Most of the studies included participants with lower urinary tract symptoms (LUTS) of a total IPSS more than 8 ([Kawabe 2006a](#); [Manjunatha 2016a](#); [Masuda 2012](#); [Matsukawa 2016](#); [Miyakita 2010](#); [Natarajan 2015](#); [Pande 2014](#); [Shirakawa 2013](#); [Takeshita 2016](#); [Watanabe 2011](#); [Yamaguchi 2013](#); [Yamanishi 2011](#); [Yokoyama 2011](#); [Yokoyama 2012](#)). Participants with IPSS more than 13 were included in three studies ([Chapple 2011](#); [Marks 2009](#); [Yu 2011](#)). Two studies (abstract [Jung 2012](#), protocol [NCT00793819](#)) did not specify the inclusion criteria for LUTS in detail. Eight out of 19 studies included participants with a prostate volume greater than 20 mL ([Kawabe 2006a](#); [Masuda 2012](#); [Matsukawa 2016](#); [Miyakita 2010](#); [Shirakawa 2013](#); [Takeshita 2016](#); [Yamanishi 2011](#); [Yu 2011](#)). Nine studies used 15mL/s or less in Qmax as an inclusion criterion ([Chapple 2011](#); [Kawabe 2006a](#); [Manjunatha 2016a](#); [Marks 2009](#); [Matsukawa 2016](#); [Miyakita 2010](#); [Shirakawa 2013](#); [Yamanishi 2011](#); [Yu 2011](#)). Major exclusion criteria included LUTS from any cause other than benign prostatic hyperplasia (BPH), prior treatment with other BPH medical therapy, recent acute urinary retention (AUR), raised prostate-specific antigen (PSA) level suspicious of prostate cancer, a history of prostate cancer or prior prostate-related surgery. [Chapple 2011](#) excluded men with improvement in the IPSS total score of 25% or more in the run-in period and [Marks 2009](#) excluded 615 participants due to adverse events, investigator recommendation, lack of efficacy, loss-to-follow-up, protocol violation, voluntary withdrawal, or other issues during the run-in period.

Intervention(s) and comparator(s)

Silodosin was administered as an oral dose of 8 mg (8 mg once daily or 4 mg twice daily) in all studies except one ([Takeshita 2016](#); 4 mg once daily). Two studies titrated the drug dose (4 mg followed by 8 mg) during the study period ([Masuda 2012](#); [Matsukawa 2016](#)).

Four agents, namely placebo, tamsulosin, naftopidil, and alfuzosin were used as comparators. All comparators were administered orally. Placebo was administered in accordance with frequencies of silodosin ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#); [NCT00793819](#)). Tamsulosin was administered as an oral dose of 0.2 mg ([Jung 2012](#); [Kawabe 2006a](#); [Miyakita 2010](#); [Takeshita 2016](#); [Watanabe 2011](#); [Yokoyama 2011](#); [Yokoyama 2012](#); [Yu 2011](#)) or 0.4 mg once daily ([Chapple 2011](#); [Manjunatha 2016a](#); [Natarajan 2015](#); [Pande 2014](#)). One study did not specify the exact dose of tamsulosin ([Yamanishi 2011](#)). Naftopidil was administered as an oral dose of 50 mg ([Shirakawa 2013](#); [Yokoyama 2011](#)) or 75 mg once daily ([Yamaguchi 2013](#)). Two studies titrated the drug dose (50 mg followed by 75 mg) during the study period ([Masuda 2012](#); [Matsukawa 2016](#)). Alfuzosin was administered as an oral dose of 10 mg once daily ([Jung 2012](#); [Manjunatha 2016a](#)).

The duration of intervention was 12 weeks in 11 (of 19) studies (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Marks 2009; Matsukawa 2016; Natarajan 2015; Pande 2014; NCT00793819; Yamaguchi 2013; Yokoyama 2011; Yu 2011). Jung 2012 and Shirakawa 2013 followed the participants for four weeks and eight weeks only, respectively. Yamanishi 2011 reported 12-month follow-up data. For cross-over trials, three (Miyakita 2010; Takeshita 2016; Watanabe 2011), one (Masuda 2012), and one study (Yokoyama 2012) reported 4 weeks', 6 weeks', and 12 weeks' follow-up outcomes before the cross-over, respectively.

Comparisons

We included four comparisons in this review: four studies compared silodosin to placebo (Chapple 2011; Kawabe 2006a; Marks 2009; NCT00793819). Thirteen (Chapple 2011; Jung 2012; Kawabe 2006a; Manjunatha 2016a; Miyakita 2010; Natarajan 2015; Pande 2014; Takeshita 2016; Watanabe 2011; Yamanishi 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) compared silodosin to tamsulosin, five (Masuda 2012; Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) compared silodosin to naftopidil, and two studies (Jung 2012; Manjunatha 2016a) compared silodosin to alfuzosin. All studies used silodosin, placebo, or other ABs as monotherapy. There were no trials that compared combination therapy with silodosin or any 5-ARIs to combination therapy with other ABs and any 5-ARIs.

Outcomes

We identified all primary outcomes in each of the included studies for four comparisons. No trial reported on our predefined secondary outcomes of AUR or surgical intervention for LUTS/BPH. However, we were able to obtain additional information by contact with the study authors (Chapple 2011; Pande 2014; Yamaguchi 2013; Yokoyama 2011) which we used for the data analysis across three comparisons. Given the nature of cross-over design studies, we assumed they were not applicable to the outcomes of AUR and surgical intervention for LUTS/BPH for the analysis. Other secondary outcomes were reported in at least one of the included studies.

Funding sources and conflicts of interest

Four reported no funding source (Jung 2012; Kawabe 2006a; Manjunatha 2016a; Yokoyama 2012), and five were supported

by pharmaceutical companies (Chapple 2011; Marks 2009; NCT00793819; Pande 2014; Yu 2011). The remaining did not mention a funding source.

Nine studies reported no conflicts of interest (Kawabe 2006a; Manjunatha 2016a; Pande 2014; Shirakawa 2013; Takeshita 2016; Watanabe 2011; Yamaguchi 2013; Yokoyama 2011; Yokoyama 2012), and four reported having relationships with pharmaceutical companies (Chapple 2011; Marks 2009; NCT00793819; Yu 2011). The remaining did not mention conflicts of interest.

Excluded studies

We excluded 23 studies (24 records) out of 58 studies (80 records) after evaluation of the full-text publications. Seven studies were reviews (Abramowicz 2009; Alcántara Montero 2016; Curran 2011; Montorsi 2010; Montorsi 2013; Prescrire Int 2011; Prescrire Int 2012). Six studies had the wrong comparator (Cakiroglu 2016; JPRN-UMIN000007917; Matsukawa 2012; Matsukawa 2017; Yoshida 2017; Yoshihisa 2012). Each of four studies had the wrong study design (Araki 2013; Boeri 2016; Chapple 2009; Kawabe 2006b) and wrong study outcome (Kobayashi 2008; Kobayashi 2009; Manjunatha 2016b; Zhou 2011), respectively. Two studies had the wrong population (Michel 2011; Roehrborn 2009). Details of excluded studies are presented elsewhere (see [Characteristics of excluded studies](#)).

Studies awaiting classification and ongoing trials

We found 12 studies awaiting classification (CTRI/2010/091/000526; Devana 2014; Jha 2015; JPRN-UMIN000003125; JPRN-UMIN000005151; JPRN-UMIN000008538; JPRN-UMIN000011556; Mandal 2013; Manohar 2014; Miyamae 2011; NCT01222650; Pawar 2015) that did not provide usable outcome data and two ongoing studies (JPRN-UMIN000003609; CTRI/2013/10/004112). Details of studies awaiting classification and ongoing trials are presented elsewhere (see [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#)).

Risk of bias in included studies

See [Figure 2](#); [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. 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)	Blinding of outcome assessment (detection bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Incomplete outcome data (attrition bias): Urologic symptom scores/ QoL	Incomplete outcome data (attrition bias): Treatment withdrawal for any reason	Incomplete outcome data (attrition bias): Treatment withdrawal due to adverse events	Incomplete outcome data (attrition bias): AUR/ surgical intervention	Incomplete outcome data (attrition bias): Cardiovascular adverse events	Incomplete outcome data (attrition bias): Sexual adverse events	Selective reporting (reporting bias)	Other bias
Chapple 2011	+	+	+	?	+	+	+	+	+	+	+	-	?
Jung 2012	?	?	-	-	+	?	?	?	?	?	?	?	?
Kawabe 2006a	?	?	?	?	+	+	?	+	?	+	+	-	-
Manjunatha 2016a	+	+	-	-	+	+	+	+	?	+	?	+	-
Marks 2009	+	+	+	+	+	?	+	+	?	+	+	+	-
Masuda 2012	-	?	?	?	+	-	+	+	?	?	?	?	?
Matsukawa 2016	+	?	-	-	+	?	+	+	?	?	?	?	+
Miyakita 2010	?	?	?	?	+	-	+	+	?	+	+	?	?
Natarajan 2015	?	?	?	?	+	?	?	?	?	?	?	-	?
NCT00793819	?	?	+	+	+	?	+	+	+	+	+	+	?
Pande 2014	+	+	-	-	+	?	+	+	+	+	+	+	+
Shirakawa 2013	+	?	-	-	+	+	+	+	?	+	+	+	+
Takeshita 2016	+	+	-	-	+	?	+	+	?	+	+	+	?

Figure 3. (Continued)

Takeshita 2016													
Watanabe 2011													
Yamaguchi 2013													
Yamanishi 2011													
Yokoyama 2011													
Yokoyama 2012													
Yu 2011													

Allocation

Random sequence generation

- We rated 10 studies as low risk of bias (Chapple 2011; Manjunatha 2016a; Marks 2009; Matsukawa 2016; Pande 2014; Shirakawa 2013; Takeshita 2016; Yamaguchi 2013; Yokoyama 2011; Yokoyama 2012) and one study as high risk of bias (Masuda 2012). The remaining were judged as unclear risk of bias.

Allocation concealment

- We rated six studies as low risk of bias (Chapple 2011; Manjunatha 2016a; Marks 2009; Pande 2014; Takeshita 2016; Yokoyama 2011) and the remaining as unclear risk of bias.

Blinding

Blinding of participants and personnel

- We rated four studies as low risk of bias (Chapple 2011; Marks 2009; NCT00793819; Yu 2011). We judged 10 studies (Jung 2012; Manjunatha 2016a; Matsukawa 2016; Pande 2014; Shirakawa 2013; Takeshita 2016; Watanabe 2011; Yamaguchi 2013; Yokoyama 2011; Yokoyama 2012) as high risk of bias and the remaining as unclear risk of bias.

Blinding of outcome assessment

- Subjective outcomes: we rated three studies as low risk of bias for subjective outcomes (Marks 2009; NCT00793819; Yu 2011). We judged nine studies (Jung 2012; Manjunatha 2016a; Matsukawa 2016; Pande 2014; Shirakawa 2013; Takeshita 2016; Watanabe 2011; Yamaguchi 2013; Yokoyama 2012) as high risk of bias and the remaining as unclear risk of bias for subjective outcomes. (Subjective outcomes: urologic symptom scores, quality of life, treatment withdrawal for any reason, treatment withdrawal due to adverse events, cardiovascular adverse events, and sexual adverse events.)
- Objective outcomes: we rated all studies as low risk of bias for objective outcomes because objective outcomes are not likely to be affected by lack of blinding. (Objective outcomes: AUR and surgical intervention for LUTS/BPH.)

Incomplete outcome data

- Urologic symptom scores and quality of life: we rated four studies as low risk of bias (Chapple 2011; Kawabe 2006a;

Manjunatha 2016a; Shirakawa 2013). We judged four studies (Masuda 2012; Miyakita 2010; Yamaguchi 2013; Yamanishi 2011) as high risk of bias and the remaining as unclear risk of bias.

- Treatment withdrawal for any reason: we rated 16 studies (Chapple 2011; Manjunatha 2016a; Marks 2009; Masuda 2012; Matsukawa 2016; Miyakita 2010; NCT00793819; Pande 2014; Shirakawa 2013; Takeshita 2016; Watanabe 2011; Yamaguchi 2013; Yamanishi 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) as low risk of bias and three studies (Jung 2012; Kawabe 2006a; Natarajan 2015) as unclear risk of bias. None of the studies were rated as high risk of bias.
- Treatment withdrawal due to adverse events: we rated 14 studies (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Marks 2009; Masuda 2012; Matsukawa 2016; Miyakita 2010; NCT00793819; Pande 2014; Shirakawa 2013; Takeshita 2016; Watanabe 2011; Yamaguchi 2013; Yokoyama 2012) as low risk of bias and the remaining studies as unclear risk of bias.
- AUR and surgical intervention for LUTS/BPH: we rated four studies (Chapple 2011; NCT00793819; Pande 2014; Yamaguchi 2013) as low risk of bias and the remaining studies as unclear risk of bias.
- Cardiovascular adverse events: we rated 11 studies (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Marks 2009; Miyakita 2010; NCT00793819; Pande 2014; Shirakawa 2013; Takeshita 2016; Yamaguchi 2013; Yokoyama 2012) as low risk of bias and the remaining studies as unclear risk of bias.
- Sexual adverse events: we rated 11 studies (Chapple 2011; Kawabe 2006a; Marks 2009; Miyakita 2010; NCT00793819; Pande 2014; Shirakawa 2013; Takeshita 2016; Yamaguchi 2013; Yokoyama 2011; Yokoyama 2012) as low risk of bias and the remaining studies as unclear risk of bias.

Selective reporting

- We rated six studies as low risk of bias (Manjunatha 2016a; Marks 2009; NCT00793819; Pande 2014; Shirakawa 2013; Takeshita 2016). We judged three studies (Chapple 2011; Kawabe 2006a; Natarajan 2015) as high risk of bias and the remaining as unclear risk of bias.

Other potential sources of bias

- We rated five studies as low risk of bias (Matsukawa 2016; Pande 2014; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2012). We judged five studies (Kawabe 2006a; Manjunatha 2016a; Marks

2009; Yokoyama 2011; Yu 2011) as high risk of bias due to clinically important imbalances in baseline characteristics and high exclusion rates after placebo run-in periods; the remaining studies were rated as unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Silodosin compared to placebo for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term); **Summary of findings 2** Silodosin compared to tamsulosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term); **Summary of findings 3** Silodosin compared to naftopidil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term); **Summary of findings 4** Silodosin compared to alfuzosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (short term)

Details are presented elsewhere (see [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#)).

1. Silodosin versus placebo

1.1. Urologic symptom scores

We included three randomized controlled trials (RCTs) ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#)) with 1743 participants in the analysis (silodosin 1012, placebo 731). Silodosin may reduce urologic symptom scores in an appreciable number of men (MD -2.65, 95% CI -3.23 to -2.08; $I^2 = 0\%$). We rated the quality of the evidence as low, downgrading for study limitations and imprecision ([Analysis 1.1](#)).

1.2. Quality of life

We included two RCTs ([Chapple 2011](#); [Kawabe 2006a](#)) with 820 participants in the analysis (silodosin 546, placebo 274). Silodosin likely results in little or no difference in quality of life (MD -0.42, 95% CI -0.71 to -0.13; $I^2 = 57\%$). We rated the quality of the evidence as moderate, downgrading for study limitations ([Analysis 1.2](#)).

1.3. Treatment withdrawal for any reason

We included three RCTs ([Chapple 2011](#); [Marks 2009](#); [NCT00793819](#)) with 1703 participants in the analysis (silodosin 958, placebo 745). Silodosin may result in little or no difference in treatment withdrawal for any reason (RR 1.08, 95% CI 0.70 to 1.66; $I^2 = 42\%$). We rated the quality of the evidence as low, downgrading for study limitations and imprecision ([Analysis 1.3](#)).

1.4. Treatment withdrawal due to adverse events

We included four RCTs ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#); [NCT00793819](#)) with 1967 participants in the analysis (silodosin 1133, placebo 834). Silodosin likely increases treatment withdrawal due to adverse events (RR 2.29, 95% CI 1.41 to 3.72; $I^2 = 0\%$). Assuming a baseline risk of treatment withdrawal due to adverse events to be 13.0% ([Preston 2000](#)), silodosin would result in 168 more treatment withdrawals per 1000 men (95% CI 53 more to 354 more). We rated the quality of the evidence as moderate, downgrading for study limitations ([Analysis 1.4](#)).

1.5. AUR

We included two RCTs ([Chapple 2011](#); [NCT00793819](#)) with 780 participants in the analysis (silodosin 492, placebo 288). We found no event for AUR in either study group.

1.6. Surgical intervention for LUTS/BPH

We included two RCTs ([Chapple 2011](#); [NCT00793819](#)) with 780 participants in the analysis (silodosin 492, placebo 288). We found no event for surgical intervention for LUTS/BPH in either study group.

1.7. Cardiovascular adverse events

We included four RCTs ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#); [NCT00793819](#)) with 1967 participants in the analysis (silodosin 1133, placebo 834). We are uncertain about the effect of silodosin on cardiovascular adverse events (RR 1.28, 95% CI 0.67 to 2.45; $I^2 = 55\%$). We rated the quality of the evidence as very low, downgrading for study limitations, inconsistency, and imprecision ([Analysis 1.5](#)).

1.8. Sexual adverse events

We included four RCTs ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#); [NCT00793819](#)) with 1967 participants in the analysis (silodosin 1133, placebo 834). Silodosin likely increases sexual adverse events (RR 26.07, 95% CI 12.36 to 54.97; $I^2 = 0\%$). Silodosin would result in 180 more sexual adverse events per 1000 men (95% CI 82 more to 388 more). We rated the quality of the evidence as moderate, downgrading for study limitations ([Analysis 1.6](#)).

Subgroup analysis

We were unable to perform any predefined subgroup analyses because there were no relevant data in the included studies. While we found pooled analyses ([Novara 2015](#)) from two included studies ([Chapple 2011](#); [Marks 2009](#)) that evaluated the efficacy and safety of silodosin versus placebo, we were unable to replicate these analyses ourselves.

Sensitivity analysis

We rated three RCTs ([Chapple 2011](#); [Marks 2009](#); [NCT00793819](#)) as low risk of bias and reanalyzed the data focused on these studies alone.

- Urologic symptom scores: we found an MD of -2.60 (95% CI -3.28 to -1.92) with the studies rated as low risk of bias ([Chapple 2011](#); [Marks 2009](#)) versus an MD of -2.65 (95% CI -3.23 to -2.08) with all included studies ([Chapple 2011](#); [Kawabe 2006a](#); [Marks 2009](#)).
- Quality of life: we found an MD of -0.30 (95% CI -0.51 to -0.09) with the study rated as low risk of bias ([Chapple 2011](#)) versus an MD of -0.42 (95% CI -0.71 to -0.13) with all included studies ([Chapple 2011](#); [Kawabe 2006a](#)).
- Treatment withdrawal for any reason: we rated all included studies as low risk of bias and we were unable to perform sensitivity analyses for this outcome.

2. Silodosin versus tamsulosin

2.1. Urologic symptom scores

We included 10 RCTs ([Chapple 2011](#); [Kawabe 2006a](#); [Manjunatha 2016a](#); [Miyakita 2010](#); [Pande 2014](#); [Takeshita 2016](#); [Yamanishi 2011](#); [Yokoyama 2011](#); [Yokoyama 2012](#); [Yu 2011](#)) with 1708 participants

in the analysis (silodosin 859, tamsulosin 849). We used the final value in one study (Pande 2014) and change from baseline in the remaining studies. Silodosin may result in little to no difference in urologic symptom scores (MD -0.04, 95% CI -1.31 to 1.24; $I^2 = 87\%$). We rated the quality of the evidence as low, downgrading for study limitations and inconsistency (Analysis 2.1).

2.2. Quality of life

We included 10 RCTs (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Miyakita 2010; Pande 2014; Takeshita 2016; Yamanishi 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) with 1707 participants in the analysis (silodosin 859, tamsulosin 848). We used the final value in two studies (Miyakita 2010; Pande 2014) and change from baseline in the remaining studies. Silodosin may result in little to no difference in quality of life (MD -0.15, 95% CI -0.53 to 0.22; $I^2 = 93\%$). We rated the quality of the evidence as low, downgrading for study limitations and inconsistency (Analysis 2.2).

2.3. Treatment withdrawal for any reason

We included 10 RCTs (Chapple 2011; Manjunatha 2016a; Natarajan 2015; Pande 2014; Takeshita 2016; Watanabe 2011; Yamanishi 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) with 1573 participants in the analysis (silodosin 788, tamsulosin 785). For the cross-over trial Watanabe 2011, we applied the conservative approach of only using the number of participants who had been initially randomized, due to lack of information about the number of participants in the analysis. We are uncertain about the effect of silodosin on treatment withdrawal for any reason (RR 1.02, 95% CI 0.62 to 1.69; $I^2 = 60\%$). We rated the quality of the evidence as very low, downgrading for study limitations, inconsistency, and imprecision (Analysis 2.3).

2.4. Treatment withdrawal due to adverse events

We included nine RCTs (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Natarajan 2015; Pande 2014; Takeshita 2016; Watanabe 2011; Yokoyama 2011; Yokoyama 2012) with 1572 participants in the analysis (silodosin 779, tamsulosin 793). For the cross-over trials Watanabe 2011 and Yokoyama 2012, we used only the number of participants who had been initially randomized due to lack of information about the number of participants in the analysis. Silodosin may or may not result in an important increase in treatment withdrawal due to adverse events (RR 1.96, 95% CI 1.12 to 3.44; $I^2 = 0\%$). Silodosin would result in 21 more treatment withdrawals for any reason per 1000 men (95% CI 3 more to 52 more). We rated the quality of the evidence as low, downgrading for study limitations and imprecision (Analysis 2.4).

2.5. AUR

We included three RCTs (Chapple 2011; Pande 2014; Yokoyama 2011) with 906 participants in the analysis (silodosin 454, tamsulosin 452). We found no event for AUR in either study group.

2.6. Surgical intervention for LUTS/BPH

We included three RCTs (Chapple 2011; Pande 2014; Yokoyama 2011) with 906 participants in the analysis (silodosin 454, tamsulosin 452). We found no event for surgical intervention for LUTS/BPH in either study group.

2.7. Cardiovascular adverse events

We included 11 RCTs (Chapple 2011; Kawabe 2006a; Manjunatha 2016a; Miyakita 2010; Natarajan 2015; Pande 2014; Takeshita 2016; Watanabe 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) with 1955 participants in the analysis (silodosin 967, tamsulosin 988). For cross-over trials, we took all measurements from silodosin periods and all measurements from tamsulosin periods in Watanabe 2011 and analysed these as if the trial were a parallel-group trial of silodosin versus tamsulosin. However, we used only the number of participants who had been initially randomized due to lack of information about the number of participants in the analysis (Miyakita 2010; Takeshita 2016; Yokoyama 2012). Silodosin may result in little to no difference in cardiovascular adverse events (RR 0.77, 95% CI 0.53 to 1.12; $I^2 = 3\%$). We rated the quality of the evidence as low downgrading for study limitations and imprecision (Analysis 2.5).

2.8. Sexual adverse events

We included 10 RCTs (Chapple 2011; Jung 2012; Kawabe 2006a; Natarajan 2015; Pande 2014; Takeshita 2016; Watanabe 2011; Yokoyama 2011; Yokoyama 2012; Yu 2011) with 1849 participants in the analysis (silodosin 920, tamsulosin 929). For cross-over trials, we took all measurements from silodosin periods and all measurements from tamsulosin periods in Watanabe 2011. However, we used only the number of participants who had been initially randomized due to lack of information about the number of participants in the analysis (Yokoyama 2012). Silodosin likely increases sexual adverse events (RR 6.05, 95% CI 3.55 to 10.31; $I^2 = 27\%$). Silodosin would result in 141 more sexual adverse events per 1000 men (95% CI 71 more to 261 more). We rated the quality of the evidence as moderate, downgrading for study limitations (Analysis 2.6).

Subgroup analysis

We found one cross-over trial that reported subgroup analyses according to age (70 years or older) and symptom severity (IPSS 20 or more) (Watanabe 2011). We were unable to perform preplanned subgroup analysis due to lack of information in within-study comparisons.

Sensitivity analysis

We rated only one study (Chapple 2011) as low risk of bias and were unable to perform a sensitivity analysis.

3. Silodosin versus naftopidil

3.1. Urologic symptom scores

We included five RCTs (Masuda 2012; Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 652 participants in the analysis (silodosin 325, naftopidil 327). We used final value in one study (Masuda 2012) and change from baseline in the remaining studies. Silodosin may result in little to no difference in urologic symptom scores (MD -0.85, 95% CI -2.57 to 0.87; $I^2 = 84\%$). We rated the quality of the evidence as low, downgrading for study limitations and inconsistency (Analysis 3.1).

3.2. Quality of life

We included five RCTs (Masuda 2012; Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 652 participants in the analysis (silodosin 325, naftopidil 327). We used the final values

in one study (Masuda 2012) and change from baseline in the remaining studies. Silodosin may result in little to no difference in quality of life (MD -0.17, 95% CI -0.60 to 0.27; $I^2 = 91\%$). We rated the quality of the evidence as low, downgrading for study limitations and inconsistency (Analysis 3.2).

3.3. Treatment withdrawal for any reason

We included four RCTs (Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 659 participants in the analysis (silodosin 334, naftopidil 325). Silodosin may result in little to no difference in treatment withdrawal for any reason (RR 1.25, 95% CI 0.81 to 1.93; $I^2 = 0\%$). We rated the quality of the evidence as low, downgrading for study limitations and imprecision (Analysis 3.3).

3.4. Treatment withdrawal due to adverse events

We included five RCTs (Masuda 2012; Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 738 participants in the analysis (silodosin 372, naftopidil 366). For the cross-over trial Masuda 2012, we used only the number of participants who had been initially randomized due to lack of information about the number of participants in the analysis. Silodosin may result in little to no difference in treatment withdrawal due to adverse events (RR 1.38, 95% CI 0.66 to 2.89; $I^2 = 0\%$). We rated the quality of the evidence as low downgrading for study limitations and imprecision (Analysis 3.4).

3.5. AUR

We included two RCTs (Yamaguchi 2013; Yokoyama 2011) with 180 participants in the analysis (silodosin 94, naftopidil 86). We found no event for AUR in either study group.

3.6. Surgical intervention for LUTS/BPH

We included two RCTs (Yamaguchi 2013; Yokoyama 2011) with 180 participants in the analysis (silodosin 94, naftopidil 86). We found no event for surgical intervention for LUTS/BPH in either study group.

3.7. Cardiovascular adverse events

We included five RCTs (Masuda 2012; Matsukawa 2016; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 808 participants in the analysis (silodosin 411, naftopidil 397). For cross-over trials, we took all measurements from silodosin periods and all measurements from tamsulosin periods in Masuda 2012. Silodosin may result in little to no difference in cardiovascular adverse events (RR 1.02, 95% CI 0.41 to 2.56; $I^2 = 0\%$). We rated the quality of the evidence as low downgrading for study limitations and imprecision (Analysis 3.5).

3.8. Sexual adverse events

We included four RCTs (Masuda 2012; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011) with 405 participants in the analysis (silodosin 206, naftopidil 199). For cross-over trials, we took all measurements from silodosin periods and all measurements from tamsulosin periods in Masuda 2012. Silodosin likely increases sexual adverse events (RR 5.93, 95% CI 2.16 to 16.29; $I^2 = 0\%$). Silodosin would result in 74 more sexual adverse events per 1000 men (95% CI 17 more to 231 more). We rated the quality of the

evidence as moderate, downgrading for study limitations (Analysis 3.6).

Subgroup analysis

We were unable to perform any subgroup analyses because there were no relevant data in the included studies.

Sensitivity analysis

We rated all of the included studies as high or unclear risk of bias and were unable to perform a sensitivity analysis.

4. Silodosin versus alfuzosin

4.1. Urologic symptom scores

We included one RCT (Manjunatha 2016a) with 60 participants in the analysis (silodosin 30, alfuzosin 30). Silodosin may or may not result in a clinically important increase in urologic symptom scores (MD 3.83, 95% CI 0.12 to 7.54). We rated the quality of the evidence as low, downgrading for study limitations and imprecision (Analysis 4.1).

4.2. Quality of life

We included one RCT (Manjunatha 2016a) with 60 participants in the analysis (silodosin 30, alfuzosin 30). Silodosin likely results in little to no difference in quality of life (MD 0.14, 95% CI -0.46 to 0.74). We rated the quality of the evidence as moderate, downgrading for study limitations (Analysis 4.2).

4.3. Treatment withdrawal for any reason

We included one RCT (Manjunatha 2016a) with 60 participants in the analysis (silodosin 30, alfuzosin 30). We found no event in treatment withdrawal for any reason in either study group.

4.4. Treatment withdrawal due to adverse events

We included one RCT (Manjunatha 2016a) with 60 participants in the analysis (silodosin 30, alfuzosin 30). We found no event in treatment withdrawal due to adverse events in either study group.

4.5. AUR

We did not find any study that reported this outcome.

4.6. Surgical intervention for LUTS/BPH

We did not find any study that reported this outcome.

4.7. Cardiovascular adverse events

We included one RCT (Manjunatha 2016a) with 60 participants in the analysis (silodosin 30, alfuzosin 30). Silodosin may result in little to no difference in cardiovascular adverse events (RR 0.67, 95% CI 0.36 to 1.24). We rated the quality of the evidence as low, downgrading for study limitations and imprecision (Analysis 4.3).

4.8. Sexual adverse events

We included one RCT (Jung 2012) with 95 participants in the analysis (silodosin 48, alfuzosin 47). Silodosin likely increases sexual adverse events (RR 37.21, 95% CI 5.32 to 260.07). Assuming a baseline risk of 0.6% (Van Kerrebroec 2002), silodosin would result in 217 more sexual adverse events per 1000 men (95% CI 26 more to 1000 more). We rated the quality of the evidence as moderate, downgrading for study limitations (Analysis 4.4).

Subgroup analysis and sensitivity analysis

We were unable to perform secondary analyses because there were no relevant data or too few data in the included studies.

DISCUSSION

Summary of main results

We included 19 unique studies with 4295 randomized participants across four comparisons for short-term follow-up. All studies included men aged over 40 years. The mean age and IPSS of the participants were 66.5 years and 19.1, respectively.

Silodosin versus placebo

Silodosin may reduce urologic symptom scores in an appreciable number of men but not improve quality of life appreciably. Treatment withdrawals for any reason do not appear increased. We are uncertain about the effect of silodosin on cardiovascular adverse events but silodosin likely increases sexual adverse events. There were no clinically important changes in treatment effects in a sensitivity analysis focused on low risk of bias studies.

Silodosin versus tamsulosin

Silodosin may result in little to no differences in urologic symptom scores and quality of life. We are uncertain about rates of treatment withdrawal for any reason. Silodosin may result in little to no difference in cardiovascular adverse events but likely increases sexual adverse events substantially.

Silodosin versus naftopidil

Silodosin may have similar effects in urologic symptom scores, quality of life, rates of treatment withdrawal for any reason and cardiovascular adverse events. Silodosin likely increases sexual adverse events substantially.

Silodosin versus alfuzosin

Silodosin may or may not result in a clinically important increase in urologic symptom scores and likely results in little to no difference in quality of life. We found no event in treatment withdrawal for any reason. Silodosin may not reduce cardiovascular adverse events but likely increases sexual adverse events substantially.

We were unable to perform any of the predefined subgroup analyses.

Overall completeness and applicability of evidence

There were a several limitations that related to overall completeness and applicability of evidence that deserve consideration.

- Our ability to assess the longer-term outcomes of silodosin compared to other drugs was limited given that follow-up duration in almost all studies (18 of 19) was 12 weeks or less. Given the long-term use of ABs for the treatment of LUTS/BPH in clinical practice, examining the efficacy and safety of silodosin over such a short term appears insufficient to provide assurance of long-term outcomes.
- Three of the larger trials included in this review used pre-randomization run-in periods (Chapple 2011; Marks 2009; Yu 2011). This may have led to the exclusion of men who were less

likely to be compliant or more prone to experiencing adverse events, thereby limiting generalizability.

- We were unable to determine the effect of silodosin on AUR or surgical interventions due to the lack of events in the included studies. This once again relates to the short follow-up period. Additional information may have to be drawn from longer-term observational studies.
- Rates of adverse events in two studies available in abstract form only were higher than those reported in full-text studies, raising concern about publication bias (Jung 2012; Yamanishi 2011).
- Although ABs such as silodosin are commonly used in combination with 5-ARIs, we did not find any eligible studies.

Quality of the evidence

We consistently downgraded the quality of the evidence by one or two steps to moderate or low. The most common reasons for downgrading were study limitations (issues surrounding allocation concealment and blinding), inconsistency (as reflected by high I^2 -values), which we were unable to explain through secondary analyses, and imprecision (wide confidence intervals that crossed the assumed threshold of clinically important difference or due to few events).

Potential biases in the review process

Despite a comprehensive search strategy without any publication or language restrictions, it is possible that we may have missed relevant publications. A majority of studies originated from Japan and India. It is possible that some, in particular negative studies were published in non-indexed journals or presented at local meetings only and therefore may have escaped our search, resulting in potential publication bias. The number of studies included in this review were insufficient to generate funnel plots; therefore, the risk of publication bias may have been underestimated. A future update of this review should consider the inclusion of regional bibliographic databases to further enhance the search.

We attempted to contact all the study authors on several occasions seeking feedback. While we received additional information from nine study authors, others did not reply. This may represent a source of bias.

For cross-over trials, we tried to extract the data before cross-over, as if the study were a parallel-group trial, in accordance with *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). However, two cross-over trials reported adverse events using all measurements from silodosin periods and all measurements from tamsulosin periods (Masuda 2012; Watanabe 2011). This may have given rise to a unit of analysis error. For other cross-over trials, we used the number of participants initially randomized as a more conservative approach. In addition, one cross-over trial used the event rate to report individual adverse events, which may also result in a unit of analysis error (double counting) (Masuda 2012).

Agreements and disagreements with other studies or reviews

To date, no published systematic review exists that focuses on silodosin and has applied the same rigorous methodology as this Cochrane Review, which includes a published protocol, a focus on

patient-important outcomes, an exhaustive literature search and an assessment of the quality of the evidence using GRADE.

In a recently reported systematic review and meta-analysis, a variety of ABs including silodosin were found to have a similar efficacy compared to placebo but were associated with significantly higher incidences of total adverse events and treatment withdrawal (Novara 2013; Yuan 2015). On the other hand, Ding 2013 reported no significant difference in the incidence of ejaculation disorder between the silodosin and tamsulosin groups, but we are concerned that the numbers used in the meta-analysis were not accurate. A systematic review of naftopidil reported that silodosin had comparable efficacy with naftopidil but was associated with a higher incidence of sexual adverse events (Castiglione 2014). However, no meta-analysis was reported and the authors did not rate the quality of the evidence. Collectively, the results of the present review are largely consistent with those of previously published reviews compared to placebo, tamsulosin, and naftopidil.

We did not find any published systematic review comparing silodosin to alfuzosin: this review is the first.

AUTHORS' CONCLUSIONS

Implications for practice

Based on our findings, the efficacy of silodosin appears to be similar to other ABs including tamsulosin, naftopidil, and alfuzosin but

it is associated with increased sexual adverse effects, specifically abnormal ejaculation, which may be an issue for sexually active men.

Implications for research

The major shortcoming of the current evidence base for silodosin is the short time-horizon of most studies, limiting our understanding of the long-term effectiveness and safety. Given that ABs such as silodosin are used for extended periods of time, typically years, longer-term trials should be performed (and could be mandated by regulatory agencies). In their absence, observational studies may help inform this issue, however, based on a recent systematic review performed by an Evidence-Based Practice Center in the United States few informative observational studies exist (Brasure 2016). There is also a consistent need for greater methodological rigor and reporting transparency.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chapple 2011

Methods

Study design: double-blind, placebo- and active-controlled, parallel-group clinical study

Chapple 2011 (Continued)

Setting/Country: 72 hospital clinics and inpatient units in 11 countries/Europe

Dates when study was conducted: May 2006-May 2007

Participants

Inclusion criteria: men ≥ 50 years with LUTS (defined by a stable IPSS total score ≥ 13 points), bladder outlet obstruction (defined by a Qmax 4 mL/s-15 mL/s, with a minimum voided volume of ≥ 125 mL), and the evidence of satisfactory compliance with study medication (80%–120% during the placebo run-in period)

Exclusion criteria: men with improvement in the IPSS total score $\geq 25\%$ in the run-in period, PVR ≥ 250 mL, intravesical obstruction from any cause other than BPH, history of any procedure considered an intervention for BPH, active urinary tract infection or history of recurrent urinary tract infections, current prostatitis or diagnosis of chronic prostatitis, history of prostate or invasive bladder cancer, significant postural hypotension, use of 5-ARIs within 6 months, or use of an α -blocker or phytotherapy within 2 weeks before entry

Total number of participants randomly assigned: 955

Group A (Silodosin)

- number of all participants randomly assigned: 381
- age (years): 65.8 ± 7.70
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: 19.1 ± 4.2
- Qmax (mL/s): 10.78 ± 2.726

Group B (Tamsulosin)

- number of all participants randomly assigned: 384
- age (years): 65.9 ± 7.41
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: 18.9 ± 4.3
- Qmax (mL/s): 10.27 ± 2.726

Group C (Placebo)

- number of all participants randomly assigned: 190
- age (years): 66.0 ± 7.37
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: 19.3 ± 4.3
- Qmax (mL/s): 10.32 ± 2.816

Interventions

Run-in period: 4 weeks, single-blind, placebo run-in period

Group A: silodosin 8 mg once daily

Group B: tamsulosin 0.4 mg once daily

Group C: placebo once daily

Duration: 12 weeks

Outcomes

Primary outcome

- change from baseline in the total score (questions 1–7) of the IPSS

How measured: IPSS questionnaire

Chapple 2011 (Continued)

Time points measured: at screening, at baseline, and after 7, 14, 28, 56, and 84 d of treatment

Time points reported: baseline and end of study

Secondary outcome

- IPSS storage and voiding symptoms subscores
- QoL
- Qmax
- percentage of treatment responders by IPSS (decrease from baseline $\geq 25\%$) and by Qmax (increase from baseline $\geq 30\%$)

How measured: IPSS questionnaire, uroflowmetry

Time points measured: IPSS: see primary outcome/Qmax: at the same time periods as IPSS

Time points reported: baseline and end of study

Safety outcomes

How measured: adverse events, physical examination (BP, heart rate), laboratory tests, and a 12-lead electrocardiogram

Time points measured: at each visit

Time points reported: at each visit

Subgroup: a post hoc analysis was conducted in the subgroup of participants with nocturia at baseline (defined as at least two voids per night), as assessed by question 7 of the IPSS

Funding sources	Recordati Ireland Ltd
Declarations of interest	Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Christopher R. Chapple and Francesco Montorsi are consultants and researchers for Recordati. Teuvo L.J. Tammela, Manfred Wirth, Evert Koldewijn, and Eldiberto Fernandez Fernandez are researchers for Recordati
Notes	<p>Language of publication: English</p> <p>Data (unadjusted IPSS and IPSS-QoL, AUR, and surgical intervention) were given by contact with study author</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned (in a ratio of 2:2:1, with stratification by center, with blocks of five assigned to each center, produced and managed centrally by an international contract research organization)"
Allocation concealment (selection bias)	Low risk	Quote: "managed centrally by an international contract research organization"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A multicenter double-blind, placebo- and active-controlled parallel group clinical study, all study personnel and participants were blinded to treatment assignment for the entire duration of the study"
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement: no information given

Chapple 2011 (Continued)

Subjective outcomes

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Low risk	Judgement: 10/381 (2.6%) in silodosin, 8/384 (2.1%) in tamsulosin, and 5/190 (2.6%) in placebo group were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	High risk	Judgement: Protocol (NCT00359905) was revised after completion of study (2009) and percentage of treatment responders was added as secondary outcome. All primary and secondary endpoints were measured at 7, 14, 28, 56, 84 day, but only reported at 12 weeks Unadjusted data for analysis for IPSS and QoL were not reported
Other bias	Unclear risk	Judgement: 4 weeks' placebo run-in period

Jung 2012

Methods	Study design: open-label, randomized comparative study Setting/Country: not reported/South Korea Dates when study was conducted: not reported
Participants	Inclusion criteria: sexually active men with BPH Exclusion criteria: not reported Total number of participants randomly assigned: 138

Jung 2012 (Continued)

Group A (Silodosin)

- number of all participants randomly assigned: 48
- age (years): not reported
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Qmax (mL/s): not reported

Group B (Tamsulosin)

- number of all participants randomly assigned: 43
- age (years): not reported
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Qmax (mL/s): not reported

Group C (Alfuzosin)

- number of all participants randomly assigned: 47
- age (years): not reported
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Qmax (mL/s): not reported

Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 8 mg once daily</p> <p>Group B: tamsulosin 0.2 mg once daily</p> <p>Group C: alfuzosin 10 mg once daily</p> <p>Duration: 4 weeks</p>
Outcomes	<ul style="list-style-type: none"> • IPSS • Male Sexual Health Questionnaire (MSHQ) evaluating erection, ejaculation and sexual satisfaction • the percentage of participants who showed decrease in ejaculate volume or anejaculation <p>How measured: IPSS, MSHQ</p> <p>Time points measured: baseline and on the 4th week of medication</p> <p>Time points reported: baseline and on the 4th week of medication</p> <p>Subgroup: none</p>
Funding sources	None
Declarations of interest	Not reported
Notes	<p>Language of publication: English</p> <p>Publication status: abstract (full text has not been published; study author reply)</p>
Risk of bias	

Jung 2012 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label, randomized comparative study"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "open-label, randomized comparative study"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: the number of participants excluded in analysis was not reported
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: the number of participants excluded in analysis was not reported
Selective reporting (reporting bias)	Unclear risk	Judgement: protocol was not published and no information related to the review outcomes given
Other bias	Unclear risk	Judgement: abstract only

Kawabe 2006a

Methods	<p>Study design: randomized, double-blind, placebo-controlled study</p> <p>Setting/Country: 88 centers/outpatient/Japan</p> <p>Dates when study was conducted: not reported</p>
Participants	<p>Inclusion criteria: men ≥ 50 years with total IPSS of ≥ 8, an associated QoL score of ≥ 3, prostate volume (measured by transabdominal or transrectal US) of ≥ 20 mL, a Q max of < 15 mL/s with a voided volume of ≥ 100 mL and a PVR of < 100 mL</p> <p>Exclusion criteria: men who had antiandrogen preparations for 1 year before the study or had a prostatectomy, intrapelvic radiation therapy or prostatic hyperthermia (transurethral microwave hyperthermia or transurethral needle ablation). Men who had prostate cancer or suspected prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, severe bladder diverticulum, active urinary tract infection requiring medical treatment, renal impairment (serum creatinine ≥ 2.0 mg/dL) and other complications considered likely to affect micturition, severe hepatic disorders, severe cardiovascular disease and a history of orthostatic hypotension</p> <p>Total number of participants randomly assigned: 457</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 176 • age (years): 65.4 ± 7.0 • prostate volume (mL): 36.0 ± 16.9 • PSA (ng/mL): not reported • IPSS: 17.1 ± 5.7 • Qmax (mL/s): 9.89 ± 2.72 <p>Group B (Tamsulosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 192 • age (years): 65.6 ± 7.0 • prostate volume (mL): 35.7 ± 14.4 • PSA (ng/mL): not reported • IPSS: 17.0 ± 5.7 • Qmax (mL/s): 9.43 ± 2.79 <p>Group C (Placebo)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 89 • age (years): 65.0 ± 6.9 • prostate volume (mL): 35.2 ± 16.0 • PSA (ng/mL): not reported • IPSS: 17.1 ± 6.1 • Qmax (mL/s): 9.96 ± 2.65
Interventions	<p>Run-in period: none</p> <p>Group A: oral silodosin 4 mg twice daily</p> <p>Group B: oral tamsulosin 0.2 mg once daily</p> <p>Group C: oral placebo twice daily</p> <p>Duration: 12 weeks</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • change in the total IPSS from baseline

Kawabe 2006a (Continued)

How measured: IPSS questionnaire

Time points measured: at the end of wash-out period and at 1, 2, 4, 8 and 12 weeks during the treatment period

Time points reported: at the end of wash-out period and at 1, 2, and 12 weeks during the treatment period

Secondary outcome

- change in Qmax and urodynamics
- IPSS voiding and storage scores and QoL score

How measured: IPSS questionnaire, uroflowmetry

Time points measured: at the end of wash-out period and at 1, 2, 4, 8 and 12 weeks during the treatment period

Time points reported: at the end of wash-out period and 12 weeks

Safety outcomes

How measured: adverse events, physical examinations (BP and heart rate), clinical laboratory tests (hematology, blood chemistry and urine analysis)

Time points measured: at the start of the observation period and at 4 and 12 weeks of treatment (follow-up visit)

Time points reported: at the start of the observation period and at 12 weeks of treatment

Subgroup: analysis based on LUTS severity, post hoc investigation in Qmax among the 3 treatment groups in the overall subgroup of participants with a change in voided volume of < 50% before and after treatment

Funding sources	None
Declarations of interest	None
Notes	Language of publication: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized, double-blind, placebo controlled study" Judgement: the randomization method was not defined
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomized, double-blind, placebo controlled study" Judgement: placebo-controlled study, but double-blind was not clear who was blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Quote: "randomized, double-blind, placebo controlled study" Judgement: double-blind was not clear who was blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding

Kawabe 2006a (Continued)

Objective outcomes

Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Low risk	Judgement: 1/176 (0.5%) in silodosin group, 0/192 (0%) in tamsulosin, and 0/89 (0%) were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: 1/176 (0.5%) in silodosin group, 0/192 (0%) in tamsulosin, and 0/89 (0%) were not included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: 1/176 (0.5%) in silodosin group, 0/192 (0%) in tamsulosin, and 0/89 (0%) were not included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: 1/176 (0.5%) in silodosin group, 0/192 (0%) in tamsulosin, and 0/89 (0%) were not included in analysis
Selective reporting (re- porting bias)	High risk	Judgement: protocol was not published and additional post hoc subgroup investigation was not defined in method section
Other bias	High risk	Judgement: baseline imbalance in QoL; primary endpoint was adjusted analysis by baseline QoL. Drug administration times were different between groups

Manjunatha 2016a

Methods	Study design: prospective, randomized, comparative, open-label study Setting/Country: tertiary care hospital/India Dates when study was conducted: June 2013-June 2014
Participants	Inclusion criteria: men ≥ 45 years with symptomatic BPH with IPSS of ≥ 8 , QoL of ≥ 3 , and Qmax of < 15 mL/s, but > 4 mL/s with a voided volume of > 100 mL Exclusion criteria: severe hepatic or renal insufficiency, urinary tract infections, urethral stricture, neurogenic bladder, PSA ≥ 5 ng/mL, history of urethral or prostatic surgery, hypotension or severe untreated hypertension, history of esophageal or intestinal obstruction, history of multiple drug abuse, significant psychiatric problems, serious disease or malignancy, increased risk of QTc (corrected QT Interval in the heart's electrical cycle) prolongation (e.g. hypokalemia, concomitant use of Class Ia and III antiarrhythmics, antipsychotics, tricyclic antidepressants, etc.), concomitant use of 5-ARIs and strong cytochrome P450 3A4 inhibitors, likelihood of requiring catheterization within next 3 months Total number of participants randomly assigned: 90 Group A (Silodosin)

Manjunatha 2016a (Continued)

- number of all participants randomly assigned: 30
- age (years): 64.00 ± 11.14
- prostate volume (mL): 40.57 ± 16.45
- PSA (ng/mL): 1.89 ± 1.06
- IPSS: 15.93 ± 6.03
- Qmax (mL/s): 10.03 ± 3.35

Group B (Tamsulosin)

- number of all participants randomly assigned: 30
- age (years): 63.60 ± 9.05
- prostate volume (mL): 40.33 ± 21.55
- PSA (ng/mL): 2.21 ± 1.33
- IPSS: 21.63 ± 7.63
- Qmax (mL/s): 9.58 ± 3.62

Group C (Alfuzosin)

- number of all participants randomly assigned: 30
- age (years): 63.43 ± 8.91
- prostate volume (mL): 44.43 ± 27.72
- PSA (ng/mL): 2.29 ± 1.27
- IPSS: 19.2 ± 9.6
- Qmax (mL/s): 10.18 ± 3.45

Interventions

Run-in period: none

Group A: silodosin capsule 8 mg once daily in the morning (before breakfast)

Group B: tamsulosin tablet/capsule 0.4 mg (before meals) once daily at bedtime

Group C: alfuzosin sustained release tablet 10 mg (immediately after meals) once daily

Duration: 12 weeks

Outcomes

Primary outcome

- change in total IPSS from baseline

How measured: IPSS questionnaire

Time points measured: baseline, after 2 weeks (visit 1), 4 weeks (visit 2), 8 weeks (visit 3), and 12 weeks (visit 4)

Time points reported: baseline, after 2 weeks (visit 1), 4 weeks (visit 2), 8 weeks (visit 3), and 12 weeks (visit 4)

Secondary outcome

- change in Qmax
- subjective symptom scores of IPSS (voiding and storage scores)
- QoL

How measured: uroflowmetry, IPSS questionnaire

Time points measured: baseline, after 2 weeks (visit 1), 4 weeks (visit 2), 8 weeks (visit 3), and 12 weeks (visit 4)

Time points reported: baseline, after 2 weeks (visit 1), 4 weeks (visit 2), 8 weeks (visit 3), and 12 weeks (visit 4)

Manjunatha 2016a (Continued)

Safety outcomes

How measured: side effects, cardiovascular parameters, pulse rate, and BP (supine and standing)

Time points measured: baseline, after 2 weeks (visit 1), 4 weeks (visit 2), 8 weeks (visit 3), and 12 weeks (visit 4)

Time points reported: cumulative results from follow-up visits

Subgroup: none

Funding sources	None
Declarations of interest	None
Notes	Language of publication: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "prospective, randomized". Judgement: random number table in protocol
Allocation concealment (selection bias)	Low risk	Judgement: no information in article, but "Sequentially numbered, sealed, opaque envelopes" in protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: open-label randomized study
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Judgement: open-label randomized study
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Low risk	Quote: "there were no drop-outs or protocol violations during the study and all the ninety subjects were included in the analysis"
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Quote: "there were no drop-outs or protocol violations during the study and all the ninety subjects were included in the analysis"
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Quote: "there were no drop-outs or protocol violations during the study and all the ninety subjects were included in the analysis"
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given

Manjunatha 2016a (Continued)

Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Quote: "there were no drop-outs or protocol violations during the study and all the ninety subjects were included in the analysis"
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: the number of participants with sexual adverse events in tamsulosin and alfuzosin group were not reported
Selective reporting (reporting bias)	Low risk	Judgement: protocol (Clinical Trials Registry-India (CTRI/2013/07/003805)) was published and the prespecified outcomes were well described.
Other bias	High risk	Judgement: probably, baseline imbalance in IPSS score, PSA, PVR (silodosin group has markedly lower) and prostate volume (alfuzosin group has markedly higher prostate volume).

Marks 2009

Methods	<p>Study design: parallel-group, double-blind, randomized study</p> <p>Setting/Country: multicenter/USA</p> <p>Dates when study was conducted: May 2005-August 2006</p>
Participants	<p>Inclusion criteria: men aged ≥ 50 years with an IPSS of ≥ 13, a Qmax of 4 mL/s-15 mL/s and a PVR < 250 mL</p> <p>Exclusion criteria: men with intravesical obstruction unrelated to BPH; bladder calculi; history of or current condition affecting bladder function; prior surgical intervention to relieve BPH or bladder neck obstruction; active urinary tract infection or history of recurrent urinary tract infection within the past 2 years; prostatitis within the past 3 months; BPH-unrelated urinary retention within the past 3 months; and a history of recurring prostatitis (> 3 times within the past year), prior or current prostate cancer or PSA > 10 ng/mL; prior invasive bladder cancer; bladder catheterization or bladder or prostate instrumentation within the past 30 days and history of or current significant postural hypotension, including changes in systolic (> 30 mm Hg) or diastolic (> 20 mm Hg) BP or heart rate (more than 20 beats per minute), and lightheadedness, fainting, blurred vision, profound weakness or syncope upon change in position</p> <p>Total number of participants randomly assigned: 923</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 466 age (years): 64.6 ± 8.1 prostate volume (mL): not reported PSA (ng/mL): not reported IPSS: 21.3 ± 5.1 Qmax (mL/s): 8.7 ± 2.6 <p>Group B (Placebo)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 457 age (years): 64.7 ± 8.1 prostate volume (mL): not reported PSA (ng/mL): not reported IPSS: 21.3 ± 4.9

Marks 2009 (Continued)

- Qmax (mL/s): 8.9 ± 2.8

Interventions	<p>Run-in period: single-blind, placebo run in for 4 weeks</p> <p>Group A: silodosin 8 mg once daily with breakfast</p> <p>Group B: placebo once daily with breakfast</p> <p>Duration: 12 weeks</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • mean change from baseline to week 12 in total IPSS <p>How measured: IPSS questionnaire</p> <p>Time points measured: at weeks 0 (baseline), 0.5, 1, 2, 4 and 12</p> <p>Time points reported: at weeks 0 (baseline), 0.5, 1, 2, 4 and 12</p> <p>Secondary outcome</p> <ul style="list-style-type: none"> • mean change in Qmax from baseline to week 12 <p>How measured: uroflow assessed by study investigator and a blinded central reader</p> <p>Time points measured: at baseline, 2-6 h after the first dose, and at weeks 1, 2, 4 and 12</p> <p>Time points reported: at baseline, 2-6 h after the first dose, and at weeks 1, 2, 4 and 12</p> <p>Safety outcomes</p> <p>How measured: adverse event/additional safety assessments included 12-lead electrocardiograms, clinical laboratory tests and vital sign measurements including postural hypotension tests and physical examinations</p> <p>Time points measured: at every visit except at post-randomization week 0.5</p> <p>Time points reported: cumulative results from follow-up visits</p> <p>Subgroup: none</p>
Funding sources	Allergan, American Medical Systems, Astellas, Bayer, Beckman Coulter, Diagnostic Ultrasound, GTX, GlaxoSmithKline, Gen-Probe, Indevus, Light Sciences Oncology, Lilly/ICOS, Merck, Novartis, Onconome, Pfizer, Sanofi, Solvay, Watson, National Institutes of Health, CapCURE, Pardee Foundation and Seder Foundation
Declarations of interest	Allergan, American Medical Systems, Astellas, Bayer, Beckman Coulter, Diagnostic Ultrasound, GTX, GlaxoSmithKline, Gen-Probe, Indevus, Light Sciences Oncology, Lilly/ICOS, Merck, Novartis, Onconome, Pfizer, Sanofi, Solvay, Watson, National Institutes of Health, CapCURE, Pardee Foundation and Seder Foundation
Notes	<p>Language of publication: English</p> <p>Study author reply: "Pharmaceuticals only have the data". We cannot contact study supporter in pharmaceuticals due to wrong email address</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned (1:1) to double-blind treatment, randomization schedule using PROC PLAN in SAS."

Marks 2009 (Continued)

Allocation concealment (selection bias)	Low risk	Judgement: no information in article, but "Sequentially numbered, sealed, opaque envelopes" in protocol
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was maintained throughout the study by the use of identical medication packaging with placebo matching silodosin in size and external appearance. Emergency information labels that indicated the patient's assigned treatment were available to the investigator should knowledge of treatment assignment be needed to ensure the patient's well-being. If unblinding of the investigator, site personnel or the patient was required in a particular case that patient was to be discontinued from the study."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Blinding was maintained throughout the study by the use of identical medication packaging with placebo matching silodosin in size and external appearance. Emergency information labels that indicated the patient's assigned treatment were available to the investigator should knowledge of treatment assignment be needed to ensure the patient's well-being. If unblinding of the investigator, site personnel or the patient was required in a particular case that patient was to be discontinued from the study."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: discontinued/lost to follow-up were 53/466 (11.4%) and 38/457 (8.3%), Loss of follow-up 6/466 (1.3%) and 3/457 (0.3%), but discrepancies in the reason of discontinuation (47/466, 35/457) between intervention and placebo group. Last observations were carried forward to impute values missing for week 12
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Low risk	Judgement: protocols (NCT00224107, NCT00224120) were published and the prespecified outcomes were well described
Other bias	High risk	Judgement: single-blind placebo run-in for 4 weeks; participants with $\geq 30\%$ decrease in IPSS or an increase in Qmax of ≥ 3 mL/s during the run-in period were excluded from randomization

Masuda 2012

Methods	<p>Study design: randomized, cross-over study</p> <p>Setting/Country: multicenter/Japan</p> <p>Dates when study was conducted: November 2009-March 2011</p>
Participants	<p>Inclusion criteria: men ≥ 50 years with prostate estimated volume of $> 20 \text{ cm}^3$, IPSS of ≥ 8, a QoL score of ≥ 3 points</p> <p>Exclusion criteria: men with organic diseases other than BPH (prostate cancer, bladder tumor, prostatitis, urethral stricture, etc.), transurethral resection of prostate or minimally invasive treatment, under catheterization and under self-donating urination, active urinary tract infections, combined neuro-pathic bladder and nervous system disorder, received hormone-based prostatic hyperplasia treatment medicine 6 months before the start of the study, received androgen-receptor blocking agent 6 weeks before the study, and those judged unsuitable by the attending physician</p> <p>Total number of participants randomly assigned: 92</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 44 • age (years): 66.5 ± 5.6 • prostate volume (mL): 38.8 ± 13.1 • PSA (ng/mL): not reported • IPSS: 18.6 ± 5.5 • Qmax (mL/s): 8.0 ± 3.7 <p>Group B (Naftopidil)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 48 • age (years): 68.5 ± 5.7 • prostate volume (mL): 45.7 ± 17.8 • PSA (ng/mL): not reported • IPSS: 17.6 ± 5.0 • Qmax (mL/s): 9.3 ± 4.9
Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 2 mg-4 mg twice a day for 2 weeks in the morning and evening, and 4 mg twice daily in the morning and evening for 4 more weeks, if there were no problems such as side effects</p> <p>Group B: naftopidil 50 mg-75 mg once in the morning for 2 weeks, and if there were no problems such as side effects 75 mg was administered once in the morning for 4 more weeks</p> <p>Duration: 6 weeks (before cross-over)/total 12 weeks</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • total score of IPSS <p>How measured: IPSS questionnaire</p> <p>Time points measured: before and after treatment (6 weeks and 12 weeks)</p> <p>Time points reported: before and after treatment (6 weeks and 12 weeks)</p> <p>Secondary outcome</p> <ul style="list-style-type: none"> • IPSS subscore

Masuda 2012 (Continued)

- QoL score
- OABSS
- Qmax
- PVR
- participant preference for the drug

How measured: IPSS: IPSS questionnaire/OABSS: OABSS questionnaire/PVR: abdominal US/patient preference: questionnaire survey

Time points measured: before administration of the drug and 4 weeks, 8 weeks

Time points reported: before administration of the drug and 4 weeks, 8 weeks

Safety outcomes

How measured: adverse events

Time points measured: not reported

Time points reported: at the end of study (12 weeks)

Subgroup: none

Funding sources	Not reported
Declarations of interest	Not reported
Notes	Language of publication: Japanese No wash-out period between cross-over

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "all patients who got consent were assigned in turn to 'Naf-Silo group' and 'Silo-Naf group' alternately"
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	High risk	Judgement: 14/44 (31.9%) and 14/48 (29.2%) participants in the silodosin and naftopidil group were not included in the analysis

Masuda 2012 (Continued)

Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: not available (cross-over trial)
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: 5/88 (5.7%) and 17/96 (17.8%) participants in the silodosin and tamsulosin group were not included in the analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: 5/88 (5.7%) and 17/96 (17.8%) participants in the silodosin and tamsulosin group were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: prespecified study outcomes were well described but protocol was not published
Other bias	Unclear risk	Judgement: no wash-out period

Matsukawa 2016

Methods	<p>Study design: prospective, open-label, randomized study</p> <p>Setting/Country: 52 urologists participated at a total of 44 investigational sites/outpatients/Japan</p> <p>Dates when study was conducted: May 2012-September 2013</p>
Participants	<p>Inclusion criteria: men with total IPSS 8 or greater, IPSS QoL score 3 or greater, total OABSS 3 or greater, 1 or more urinary urgency episodes per week, prostate volume 20 ml or greater on transabdominal US, Qmax less than 15 ml per second at a voided volume of 100 ml or greater and PVR less than 150 ml, and age 50 years or greater</p> <p>Exclusion criteria: men received oral treatment with α1-blockers, anticholinergic agents, 5α-reductase inhibitors, antidepressants, anti-anxiety agents or sex hormonal agents, they had neurogenic bladder dysfunction, bladder calculi or active urinary tract infection, severe cardiac disease, renal dysfunction (serum creatinine levels 2 mg/dl or more) or hepatic dysfunction (aspartate and alanine aminotransferase concentrations more than twice normal values)</p> <p>Total number of participants randomly assigned: 350</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 175 • age (years): 70.6 $\pm$ 7.8 • prostate volume (mL): 39.6 $\pm$ 16.7 • PSA (ng/mL): 3.0 $\pm$ 3.1 • IPSS: 18.8 $\pm$ 6.2 • Qmax (mL/s): 8.2 $\pm$ 3.6

Matsukawa 2016 (Continued)

Group B (Naftopidil)

- number of all participants randomly assigned: 175
- age (years): 70.3 ± 7.8
- prostate volume (mL): 38.6 ± 14.8
- PSA (ng/mL): 3.0 ± 3.1
- IPSS: 18.9 ± 6.1
- Qmax (mL/s): 8.4 ± 3.0

Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 4 mg per day for 4 weeks, followed by 8 mg per day for 8 weeks</p> <p>Group B: naftopidil 50 mg per day for 4 weeks, followed by 75 mg per day for 8 weeks</p> <p>Duration: 12 weeks</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • changes in IPSS • changes in IPSS QoL • changes in OABSS <p>How measured: IPSS and OABSS questionnaire</p> <p>Time points measured: baseline 4 and 12 weeks after the start of treatment</p> <p>Time points reported: baseline 4 and 12 weeks after the start of treatment</p> <p>Secondary outcome</p> <ul style="list-style-type: none"> • changes in Qmax • changes in PVR <p>How measured: uroflowmetry</p> <p>Time points measured: baseline 4 and 12 weeks after the start of treatment</p> <p>Time points reported: baseline 4 and 12 weeks after the start of treatment</p> <p>Safety outcomes</p> <p>How measured: not reported</p> <p>Time points measured: not reported</p> <p>Time points reported: not reported</p> <p>Subgroup: none</p>
Funding sources	Not reported
Declarations of interest	Not reported
Notes	Language of publication: English
Risk of bias	
Bias	Authors' judgement Support for judgement

Matsukawa 2016 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization using a random number table"
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, open label, randomized"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "prospective, open label, randomized"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 18/175 (10.2%) and 18/175 (10.2%) participants in silodosin and naftopidil group were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all subjects who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all subjects who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: information was partly reported (the number of withdrawal due to cardiovascular adverse events were only reported)
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: no information given
Selective reporting (reporting bias)	Unclear risk	Judgement: prespecified outcomes were well described, but protocol was not published
Other bias	Low risk	Judgement: not detected

Miyakita 2010

Methods	Study design: randomized, cross-over study	
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Miyakita 2010 (Continued)

Setting/Country: multicenter/Japan

Dates when study was conducted: May 2006-July 2007

Participants
Inclusion criteria: men with IPSS ≥ 8 points; QoL score ≥ 3 points; prostate volume measured by US ≥ 20 mL; void volume ≥ 100 mL; and Qmax < 15 mL/s

Exclusion criteria: already used any $\alpha 1$ -blocker for the treatment of hypertension; taking vardenafil hydrochloride hydrate; and otherwise judged by an attending physician to be inappropriate

Total number of participants randomly assigned: 97

Group A (Silodosin)

- number of all participants randomly assigned: 46
- age (years): 68.2 ± 8.6
- prostate volume (mL): 41.3 ± 25.3
- PSA (ng/mL): not reported
- IPSS: 16.6 ± 5.2
- Qmax (mL/s): 9.4 ± 3.5

Group B (Tamsulosin)

- number of all participants randomly assigned: 51
- age (years): 70.1 ± 8.9
- prostate volume (mL): 37.8 ± 16.3
- PSA (ng/mL): not reported
- IPSS: 18.2 ± 5.8
- Qmax (mL/s): 9.7 ± 4.4

Interventions
Run-in period: none

Group A: silodosin 8 mg/d (4 mg/dose, twice daily)

Group B: tamsulosin 0.2 mg/d (0.2 mg/dose, once daily)

Duration: 4 weeks (before cross-over)/total 8 weeks

Outcomes
Primary outcome

- change in total IPSS from baseline

How measured: IPSS questionnaire

Time points measured: before administration of the drug and 1, 2, 4, 6 and 8 weeks after initiation of administration

Time points reported: before administration of the drug, and 4 weeks and 8 weeks

Secondary outcome

- Qmax
- PVR
- BP
- heart rate
- participant preference for the drug

How measured: not reported

Time points measured: before administration of the drug, and 4 weeks and 8 weeks

Time points reported: before administration of the drug, and 4 weeks and 8 weeks

Miyakita 2010 (Continued)

Safety outcomes

How measured: adverse events

Time points measured: throughout the study period

Time points reported: throughout the study period

Subgroup: none

Funding sources	Not reported
Declarations of interest	Not reported
Notes	Language of publication: English No wash-out period between cross-over

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	High risk	Judgement: 12/46 (26.1%) and 20/51 (39.3%) participants in the silodosin and tamsulosin group were not included in the analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: not available (cross-over trial)

Miyakita 2010 (Continued)

Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: prespecified outcomes were well described, but protocol was not published
Other bias	Unclear risk	Judgement: no wash-out period

Natarajan 2015

Methods	<p>Study design: parallel, randomized</p> <p>Setting/Country: tertiary hospital/Tamil Nadu, India</p> <p>Dates when study was conducted: August 2013-April 2015</p>
Participants	<p>Inclusion criteria: men > 50 years with bothersome LUTS from BPH and IPSS > 7</p> <p>Exclusion criteria: history of LUTS but not BPH, AUR in past 6 months, raised PSA level at baseline, serious co-morbidity of vital organs, use of concomitant medication having anticholinergic, androgenic or estrogenic influence, on other α-adrenergic antagonists or diuretics or with a history of prostatic or per urethral surgery or substance abuse</p> <p>Total number of participants randomly assigned: 57</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 28 • age (years): 61-62 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • Qmax (mL/s): not reported <p>Group B (Tamsulosin)</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 29 • age (years): 61-62 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • Qmax (mL/s): not reported
Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 8 mg capsule once daily after dinner</p> <p>Group B: tamsulosin 0.4 mg controlled-release capsule once daily after dinner</p> <p>Duration: 12 weeks</p>

Natarajan 2015 (Continued)

Outcomes
Primary outcome

- change in the total IPSS and QoL
- change in the total QoL

How measured: IPSS questionnaire

Time points measured: baseline and 12 weeks

Time points reported: baseline and 12 weeks

Secondary outcome

- proportion of participants who became completely or relatively symptom free (IPSS < 8) after 12 weeks of treatment
- change in prostate size
- change in Qmax

How measured: IPSS, US by blinded radiologist, uroflowmetry by blinded operator

Time points measured: baseline and 12 weeks

Time points reported: symptom free and change in Qmax not reported; change in prostate size, baseline and 12 weeks

Safety outcomes

How measured: adverse affects

Time points measured: at follow-up visits (4, 8, 12 weeks)

Time points reported: cumulative results from follow-up visits

Subgroup: none

Funding sources Not reported

Declarations of interest Not reported

Notes **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement: no information given

Natarajan 2015 (Continued)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: no information given
Selective reporting (reporting bias)	High risk	Quote: "Silodosin showed a significant decrease in IPSS versus tamsulosin at 2 weeks" Judgement: protocol was not published and there was no information of 2 weeks' follow-up. Secondary endpoints (proportion of participants who became completely or relatively symptom free (IPSS < 8), changes in Qmax) were not reported
Other bias	Unclear risk	Judgement: no data on baseline characteristics

NCT00793819

Methods	Study design: parallel, randomized, double-blinded study Setting/Country: NR Dates when study was conducted: January 2009-October 2009
Participants	Inclusion criteria: men in good general health and ≥ 50 years, with symptoms of moderate-severe BPH and nocturia (≥ 2 episodes per night) Exclusion criteria: men with 1) medical conditions that would confound the efficacy evaluation 2) medical conditions in which it would be unsafe to use an alpha-blocker 3) the use of concomitant drugs that would confound the efficacy evaluation 4) the use of concomitant drugs that would be unsafe with this alpha-blocker

NCT00793819 (Continued)

Total number of participants randomly assigned: 209

Group A (Silodosin)

- number of all participants randomly assigned: 111
- age (years): 64.6 ± 8.03
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Qmax (mL/s): not reported

Group B (Placebo)

- number of all participants randomly assigned: 98
- age (years): 64.2 ± 8.92
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Qmax (mL/s): not reported

Interventions	Run-in period: not reported Group A: silodosin 8 mg daily Group B: 1 placebo capsule daily Duration: 12 weeks
Outcomes	Primary outcome <ul style="list-style-type: none"> • change in nocturia episodes How measured: not reported Time points measured: before and 12 weeks after treatment Time points reported: before and 12 weeks after treatment Secondary outcomes <ul style="list-style-type: none"> • change in QoL questionnaire responses How measured: not reported Time points measured: before and 12 weeks after treatment Time points reported: before and 12 weeks after treatment Subgroup: not reported
Funding sources	Watson Pharmaceuticals
Declarations of interest	Watson Pharmaceuticals
Notes	Language of publication: English Publication status: NCT00793819 (results in clinicaltrials.gov)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

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NCT00793819 (Continued)

Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parallel randomized double blinded (Participant, Investigator)"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "parallel randomized double blinded (Participant, Investigator)"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Low risk	Judgement: protocol (NCT00793819) was published and the prespecified outcomes were well described
Other bias	Unclear risk	Judgement: protocol only

Pande 2014

Methods	Study design: single-blind, parallel-group, randomized, controlled trial	
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Sildenafil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Pande 2014 (Continued)

Setting/Country: outpatient/tertiary care hospital/Kolkata, India

Dates when study was conducted: July 2012-June 2013

Participants

Inclusion criteria: ambulatory, treatment naïve, men > 50 years with bothersome LUTS from BPH and IPSS > 7

Exclusion criteria: history of LUTS but not BPH, AUR in past 6 months, raised PSA level at baseline, serious co-morbidity of vital organs, use of concomitant medication having anticholinergic, androgenic or estrogenic influence, on other α -adrenergic antagonists or diuretics or with a history of prostatic or per urethral surgery or substance abuse

Total number of participants randomly assigned: 61

Group A (Silodosin)

- number of all participants randomly assigned: 32
- age (years): 61.4 ± 7.88
- prostate volume (mL): 42.0 ± 19.96
- PSA (ng/mL): not reported
- IPSS: 18.4 ± 3.32
- Qmax (mL/s): 15.5

Group B (Tamsulosin)

- number of all participants randomly assigned: 29
- age (years): 62.6 ± 7.55
- prostate volume (mL): 35.6 ± 9.56
- PSA (ng/mL): not reported
- IPSS: 18.4 ± 3.94
- Qmax (mL/s): 15.9

Interventions

Run-in period: none

Group A: silodosin 8 mg capsule once daily

Group B: tamsulosin 0.4 mg controlled-release capsule once daily

Duration: 12 weeks

Outcomes

Primary outcome

- total IPSS score in addition to the QoL

How measured: IPSS questionnaire

Time points measured: at 4, 8 and 12 weeks

Time points reported: at 4, 8 and 12 weeks

Secondary outcome

- proportion of participants who became completely or relatively symptom free (IPSS < 8) after 12 weeks of treatment
- change in prostate size, in terms of volume, as assessed at US by a radiologist unaware of treatment allocation
- changes in Qmax and allied parameters assessed at uroflowmetry by a blinded operator

How measured: IPSS questionnaire, US by blinded radiologist, uroflowmetry by blinded investigator

Time points measured: baseline and 12 weeks

Pande 2014 (Continued)

Time points reported: baseline and 12 weeks

Safety outcomes

How measured: vital signs, treatment-emergent adverse events, postural hypotension and retrograde ejaculation, laboratory investigations (complete blood count, fasting plasma glucose, routine liver function tests and creatinine level)

Time points measured: lab - at baseline and study end/others - each visit

Time points reported: lab - at baseline and study end/others - cumulative results from follow up visits

Subgroup: none

Funding sources	M/s Cipla Limited, Mumbai, donated both study drugs and reimbursed part of the cost of laboratory investigations on request
Declarations of interest	None
Notes	Language of publication: English Data (IPSS, QoL, AUR, surgical intervention, cardiovascular, sexual adverse events) were given by contact with study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized in 1:1 ratio to one of the two study groups in fixed blocks of 8, using computer generated random number list"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was achieved using the serially numbered, opaque, sealed envelope technique"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blind, parallel group, randomized, controlled trial", "The capsules were removed from their commercial blister strip packaging and repackaged in air-tight, screw cap containers and suitably labelled and coded as trial medication. Repackaging was done with the help of residents not otherwise involved in the study. Capsule identity was not revealed to the patients who received the total medication in three installments" Judgement: participants were blinded, but investigator and observer might be not blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "single blind, parallel group, randomized, controlled trial", "The capsules were removed from their commercial blister strip packaging and repackaged in air-tight, screw cap containers and suitably labelled and coded as trial medication. Repackaging was done with the help of residents not otherwise involved in the study. Capsule identity was not revealed to the patients who received the total medication in three installments" Judgement: participants were blinded, but investigator and observer might be not blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	Judgement: 6/32 (18.7%) in silodosin, 2/29 (6.9%) in tamsulosin lost to follow-up: missing data were imputed by last observation carried forward strategy

Pande 2014 (Continued)

Urologic symptom scores/
QoL

Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Low risk	Judgement: all participants who were randomized in each group were included in analysis. We received the data after contacting the study author.
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Low risk	Judgement: protocol (Clinical Trials Registry-India (CTRI/2014/01/004366)) was published and the prespecified outcomes were well described. Data (AUR, surgical intervention, cardiovascular, sexual adverse events) were given by contact with study author
Other bias	Low risk	Judgement: not detected

Shirakawa 2013

Methods	Study design: randomized, open-label, controlled, multicenter study Setting/Country: Kobe University School or other collaborating institutions/Japan Dates when study was conducted: July 2007-March 2011
Participants	Inclusion criteria: men with: BPH/ LUTS with a total IPSS ≥ 8 points; QoL index ≥ 3 points; Qmax < 15 mL/s; prostate volume ≥ 20 mL; and either without a history of using any $\alpha 1$ -receptor blocker (hereafter, drug-naïve group) or who had continued to use tamsulosin (0.2 mg once daily) for ≥ 3 months and wanted to switch the medication to another oral drug (hereafter, drug-switching group) Exclusion criteria: other diseases such as prostate cancer, bladder tumor, cystolithiasis, prostatitis, urethral stricture, or active urinary tract infection; complication of neurogenic bladder or disease suspected of neurogenic bladder; and whose participation in the study was deemed inappropriate by their primary physician(s) Total number of participants randomly assigned: 121 Group A (Silodosin) <ul style="list-style-type: none"> number of all participants randomly assigned: 61 age (years): 70.98 ± 6.69 prostate volume (mL): 38.24 ± 12.94

Shirakawa 2013 (Continued)

- PSA (ng/mL): not reported
- IPSS: 17.53 ± 5.4
- Qmax (mL/s): 9.87 ± 4.50

Group B (Naftopidil)

- number of all participants randomly assigned: 60
- age (years): 70.50 ± 6.58
- prostate volume (mL): 39.39 ± 25.96
- PSA (ng/mL): not reported
- IPSS: 17.56 ± 6.7
- Qmax (mL/s): 11.13 ± 6.53

Interventions	Run-in period: none Group A: silodosin 4 mg twice daily Group B: naftopidil 50 mg once daily Duration: 8 consecutive weeks	
Outcomes	<ul style="list-style-type: none">total IPSSsubtotal IPSS of storage symptomssubtotal IPSS of voiding symptomspost-micturition symptomsQoL index <p>How measured: IPSS questionnaire</p> <p>Time points measured: at baseline, 4 and 8 weeks</p> <p>Time points reported: at baseline, 4 and 8 weeks</p> <p>Safety outcomes</p> <p>How measured: adverse events</p> <p>Time points measured: not reported</p> <p>Time points reported: cumulative results from follow-up visits</p> <p>Subgroup: drug-naïve/drug-switching</p>	
Funding sources	Not reported	
Declarations of interest	None	
Notes	Language of publication: English	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned (using a random number table)"
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given

Shirakawa 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomized, open-label, controlled multicenter study" Judgement: no one was blinded (protocol)
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "randomized, open-label, controlled multicenter study" Judgement: no one was blinded (protocol)
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Low risk	Judgement: 5/61 (8.2%) and 4/60 (6.7%) participants in silodosin and naftopidil were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	2/61 (3.3%) and 3/60 (5.0%) participants in silodosin and naftopidil were not included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: 2/61 (3.3%) and 3/60 (5.0%) participants in silodosin and naftopidil were not included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: 2/61 (3.3%) and 3/60 (5.0%) participants in silodosin and naftopidil were not included in analysis
Selective reporting (reporting bias)	Low risk	Judgement: protocol (UMIN000008331) was published. While the results were shown separately in participants with drug naïve and switching group, review outcomes were well described
Other bias	Low risk	Not detected

Takeshita 2016

Methods	Study design: randomized, cross-over study Setting/Country: 4 community-based hospitals/Japan Dates when study was conducted: February 2011-July 2014
Participants	Inclusion criteria: men aged ≥ 50 years with LUTS/BPH, an IPSS of ≥ 8 , QoL score of ≥ 3 , and US-estimated prostatic volume of ≥ 20 mL

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Takeshita 2016 (Continued)

Exclusion criteria: those that had taken any alpha-blocker within the previous 28 days; those currently taking phosphodiesterase type 5 inhibitors, 5-ARIs, or antiandrogens; those with severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min per 1.73 m²); and those judged to be inappropriate by the attending physicians

Total number of participants randomly assigned: 34

Group A (Silodosin)

- number of all participants randomly assigned: 18
- age (years): 69.6 ± 5.4
- prostate volume (mL): 38.7 ± 11.6
- PSA (ng/mL): 5.9 ± 5.9
- IPSS: 17.1 ± 7.3
- Qmax (mL/s): 9.5 ± 4.9

Group B (Tamsulosin)

- number of all participants randomly assigned: 16
- age (years): 69.4 ± 7.0
- prostate volume (mL): 47.3 ± 30.4
- PSA (ng/mL): 5.4 ± 4.4
- IPSS: 15.2 ± 7.0
- Qmax (mL/s): 10.2 ± 3.8

Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 4 mg once daily in the morning</p> <p>Group B: tamsulosin 0.2 mg once daily in the morning</p> <p>Duration: 4 weeks (before cross-over)/total 8 weeks</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • changes in IPSS and QoL score <p>How measured: IPSS questionnaire</p> <p>Time points measured: baseline to weeks 4 and 8</p> <p>Time points reported: baseline to weeks 4 and 8</p> <p>Secondary outcome</p> <ul style="list-style-type: none"> • uroflowmetry • BP • changes in subjective parameters including IPSS subscores and OABSS • participant preference for the drug <p>How measured: participant preference for the drug by self-administered questionnaire</p> <p>Time points measured: before administration of the drug, and 4 weeks and 8 weeks</p> <p>Time points reported: before administration of the drug, and 4 weeks and 8 weeks</p> <p>Safety outcomes</p> <p>How measured: adverse events</p> <p>Time points measured: baseline to weeks 4 and 8</p>

Takeshita 2016 (Continued)

Time points reported: baseline to weeks 4 and 8

Subgroup: none

Funding sources	Not reported
Declarations of interest	None
Notes	<p>Language of publication: English</p> <p>No wash-out period between cross-over</p> <p>Data (IPSS, QoL, treatment withdrawal, cardiovascular, sexual adverse events) were given by contact with study author</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement: author reply "random number table"
Allocation concealment (selection bias)	Low risk	Judgement: author reply "sealed opaque envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label, randomized crossover study"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "open-label, randomized crossover study"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 2/18 (11.2%) and 2/16 (12.5%) participants in the silodosin and tamsulosin group were not included in the analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: not available (cross-over trial)
Incomplete outcome data (attrition bias)	Low risk	Judgement: all participants who were randomized in each group were included in analysis

Takeshita 2016 (Continued)

Cardiovascular adverse
events

Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Low risk	Judgement: protocol (JPRN-UMIN000004918) was published and prespecified, study outcomes were analyzed as planned. Data (IPSS, QoL, treatment withdrawal, cardiovascular, sexual adverse events) were provided after contact with study author
Other bias	Unclear risk	Judgement: no wash-out period

Watanabe 2011

Methods	Study design: randomized, cross-over study Setting/Country: 3 institutions/Japan Dates when study was conducted: February 2008-September 2009
Participants	Inclusion criteria: men with LUTS associated with BPH and had an IPSS ≥ 8 and an IPSS-QoL score ≥ 2 Exclusion criteria: not reported Total number of participants randomly assigned: 102 Group A (Silodosin) <ul style="list-style-type: none"> number of all participants randomly assigned: 51 age (years): 69.3 ± 8.3 prostate volume (mL): 36.6 ± 18.3 PSA (ng/mL): not reported IPSS: 16.4 ± 5.0 Qmax (mL/s): 9.1 ± 5.7 Group B (Tamsulosin) <ul style="list-style-type: none"> number of all participants randomly assigned: 51 age (years): 69.9 ± 8.4 prostate volume (mL): 35.1 ± 13.0 PSA (ng/mL): not reported IPSS: 18.1 ± 6.2 Qmax (mL/s): 8.8 ± 5.2
Interventions	Run-in period: none Group A: silodosin 4 mg, orally, twice daily Group B: tamsulosin 0.2 mg, orally, once daily Duration: 4 weeks (before cross-over)/total 8 weeks
Outcomes	Primary outcome <ul style="list-style-type: none"> participant preference for the drug and reason of preference

Watanabe 2011 (Continued)

How measured: questionnaire and open question

Time points measured: 8 weeks

Time points reported: 8 weeks

Secondary outcome

- IPSS
- IPSS-QoL
- Qmax
- mean urinary flow rate
- PVR

How measured: not reported

Time points measured: baseline and at 4 and 8 weeks

Time points reported: baseline and at 4 and 8 weeks

Safety outcomes

How measured: adverse events

Time points measured: not reported

Time points reported: during the study

Subgroup: age ≥ 70 /IPSS ≥ 20

Funding sources	Not reported
Declarations of interest	None
Notes	Language of publication: English No wash-out period between cross-over

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label study"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "open-label study"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding

Watanabe 2011 (Continued)

Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 9/51 (17.7%) and 9/51 (17.7%) participants in the silodosin and tamsulosin group were not included in the analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: not available (cross-over trial)
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: 14/102 (13.8%) and 11/102 (10.8%) participants in the silodosin and tamsulosin group were not included in the analysis (study author reported the results after cross-over)
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: 14/102 (13.8%) and 11/102 (10.8%) participants in the silodosin and tamsulosin group were not included in the analysis (study author reported the results after cross-over)
Selective reporting (reporting bias)	Unclear risk	Judgement: no protocol available
Other bias	Unclear risk	Judgement: no wash-out period

Yamaguchi 2013

Methods	Study design: parallel, randomized trial Setting/Country: Nihon University School of Medicine/Japan Dates when study was conducted: December 2007-November 2010
Participants	Inclusion criteria: men with BPH $\geq$ 50 years with significant LUTS and deteriorated QoL, with IPSS of $\geq$ 8 and its QoL score of $\geq$ 3 Exclusion criteria: established prostate cancer, neurogenic bladder and any other complications that affect micturitional status; underwent prostate surgery, intervention or radiation therapy Total number of participants randomly assigned: 109 Group A (Silodosin) <ul style="list-style-type: none"> • number of all participants randomly assigned: 58 • age (years): 69.3 ± 7.8 • prostate volume (mL): 33.2 ± 21.2 • PSA (ng/mL): 2.8 ± 3.3 • IPSS: 16.9 ± 5.5 • Qmax (mL/s): 10.4 ± 5.0

Yamaguchi 2013 (Continued)

Group B (Naftopidil)

- number of all participants randomly assigned: 51
- age (years): 70.0 ± 7.0
- prostate volume (mL): 39.5 ± 18.0
- PSA (ng/mL): 3.9 ± 3.5
- IPSS: 18.9 ± 7.0
- Qmax (mL/s): 9.9 ± 5.3

Interventions	Run-in period: none Group A: silodosin 8 mg/d Group B: naftopidil 75 mg/d Duration: 12 weeks
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL • IIEF-5 • Qmax • PVR <p>How measured: questionnaire, uroflowmetry</p> <p>Time points measured: before and 4, 8, and 12 weeks after treatment</p> <p>Time points reported: IPSS, QoL, IIEF-5: before and 4, 8, and 12 weeks after treatment/Qmax, PVR: before and 12 weeks after treatment</p> <p>Subgroup: none</p>
Funding sources	Not reported
Declarations of interest	None
Notes	Language of publication: English Data (IPSS, QoL, treatment withdrawal, AUR, surgical intervention, cardiovascular adverse events) were given by contact with study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement: author reply "random number table envelope method"
Allocation concealment (selection bias)	Unclear risk	Judgement: author reply "random number table envelope method"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: author reply "not blinded"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Judgement: author reply "not blinded"

Yamaguchi 2013 (Continued)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	High risk	Judgement: 17/58 (29.3%) and 13/51 (25.5) participants in silodosin and naftopidil group were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis. We received the data after contacting the study author
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis. We received the data after contacting the study author
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Low risk	Judgement: all participants who were randomized in each group were included in analysis. We received the data after contacting the study author
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis. We received the data after contacting the study author
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all sexually active subjects (silodosin: 23/53 (44%), naftopidil: 21/44 (47%)) who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: data (treatment withdrawal, AUR, and surgical intervention) were given by contact with study author, but protocol was not published
Other bias	Low risk	Judgement: not detected

Yamanishi 2011

Methods	Study design: parallel, randomized trial Setting/Country: not reported Dates when study was conducted: not reported
Participants	Inclusion criteria: men with IPSS total score ≥ 8 , Qmax < 15 mL/s, total prostate volume measured by US > 20 mL Exclusion criteria: prostate cancer, urethral stricture, apparent neurogenic bladder and those on medication that might affect voiding function such as alpha-blockers, anticholinergics and/or antiandrogen drugs Total number of participants randomly assigned: 149 Group A (Silodosin) <ul style="list-style-type: none"> number of all participants randomly assigned: 75 age (years): 71.3 ± 8.2

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Yamanishi 2011 (Continued)

- prostate volume (mL): 42.0 ± 23.7
- PSA (ng/mL): 3.2 ± 3.6
- IPSS: 18.8 ± 7.3
- Qmax (mL/s): 7.7 ± 2.8

Group B (Tamsulosin)

- number of all participants randomly assigned: 74
- age (years): 72.2 ± 7.6
- prostate volume (mL): 41.2 ± 23.0
- PSA (ng/mL): 3.7 ± 3.7
- IPSS: 17.8 ± 6.4
- Qmax (mL/s): 8.4 ± 3.3

Interventions	Run-in period: none Group A: silodosin 4 mg twice daily Group B: tamsulosin 0.2 mg-0.4 mg daily Duration: 12 months
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL • average flow rate • Qmax • PVR <p>How measured: questionnaire, uroflowmetry</p> <p>Time points measured: before, and at 1, 3, 6 and 12 months after the therapy</p> <p>Time points reported: before, and at 1, 3, 6 and 12 months after the therapy</p> <p>Subgroup: none</p>
Funding sources	Not reported
Declarations of interest	Not reported
Notes	Language of publication: English Publication status: abstract (full text has not been published; study author reply)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement: no information given

Yamanishi 2011 (Continued)

Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	High risk	Judgement: 19/75 (25.3%) and 30/74 (40.5%) participants in silodosin and tamsulosin were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: no information given
Selective reporting (reporting bias)	Unclear risk	Judgement: protocol was not published and no information related to the review outcomes given
Other bias	Unclear risk	Judgement: abstract only

Yokoyama 2011

Methods	Study design: parallel, randomized trial Setting/Country: Kawasaki Medical School/Japan Dates when study was conducted: June 2007-December 2008
Participants	Inclusion criteria: men with LUTS aged 50–80 years and with IPSS ≥ 8 Exclusion criteria: received oral treatment with 5-ARIs, anticholinergic agents, antidepressants, or sex hormonal agents, had neurogenic bladder dysfunction, bladder calculi, or active urinary tract infection, or had severe cardiac disease, renal dysfunction (serum creatinine > 2 mg/dL), or hepatic dysfunction Total number of participants randomly assigned: 136

Yokoyama 2011 (Continued)

Group A (Silodosin)

- number of all participants randomly assigned: 45
- age (years): 70.2 ± 0.9
- prostate volume (mL): 33.3 ± 2.3
- PSA (ng/mL): not reported
- IPSS: 18.7 ± 0.7
- Qmax (mL/s): 9.03 ± 0.6

Group B (Tamsulosin)

- number of all participants randomly assigned: 45
- age (years): 71.5 ± 1.1
- prostate volume (mL): 32.5 ± 2.0
- PSA (ng/mL): not reported
- IPSS: 18.0 ± 1.1
- Qmax (mL/s): 8.56 ± 0.5

Group C (Naftopidil)

- number of all participants randomly assigned: 46
- age (years): 69.1 ± 1.2
- prostate volume (mL): 35.0 ± 3.1
- PSA (ng/mL): not reported
- IPSS: 17.4 ± 0.8
- Qmax (mL/s): 8.63 ± 0.5

Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 4 mg twice a day</p> <p>Group B: tamsulosin 0.2 mg once a day</p> <p>Group C: naftopidil 50 mg once a day</p> <p>Duration: 12 weeks</p>
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL • IIEF • Qmax • PVR <p>How measured: questionnaire (IPSS, QoL, IIEF), uroflowmetry, US (PVR)</p> <p>Time points measured: before, and 1 and 3 months</p> <p>Time points reported: before, and 1 and 3 months</p> <p>Subgroup: none</p>
Funding sources	Not reported
Declarations of interest	None (study author reply)
Notes	<p>Language of publication: English</p> <p>Data (IPSS, QoL, AUR, and surgical intervention) from study author</p>

Yokoyama 2011 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement: study author reply "Computer generated central randomization"
Allocation concealment (selection bias)	Low risk	Judgement: study author reply "Computer generated central randomization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: study author reply "participants were not blinded"
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement: no information given
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 4/45 (8.9%), 6/45 (13.3%), and 4/46 (8.7) participants in silodosin, tamsulosin, and naftopidil group were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Judgement: 4/45 (8.9%), 6/45 (13.3%), and 4/46 (8.7) participants in silodosin, tamsulosin, and naftopidil group were not included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: 4/45 (8.9%), 6/45 (13.3%), and 4/46 (8.7) participants in silodosin, tamsulosin, and naftopidil group were not included in analysis. We received the data after contacting the study author
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: 4/45 (8.9%), 6/45 (13.3%), and 4/46 (8.7) participants in silodosin, tamsulosin, and naftopidil group were not included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all sexually active subjects (silodosin: 11/45 (24.4%), tamsulosin 12/45 (26.6%), naftopidil: 15/46 (31.9%)) were included in analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: prespecified outcomes were well described and data were given by study author, but protocol was not published
Other bias	High risk	Judgement: drug administration times were different among groups. Baseline imbalance in PVR, but the fact that silodosin group had much higher PVR may underestimate the effect size

Yokoyama 2012

Methods	<p>Study design: randomized, cross-over study</p> <p>Setting/Country: single center/Japan</p> <p>Dates when study was conducted: June 2008-March 2010</p>
Participants	<p>Inclusion criteria: men aged 50 years who had a total IPSS ≥ 8 and a QoL index ≥ 3</p> <p>Exclusion criteria: prostate cancer, neurogenic bladder, urethral stricture, active urinary tract infection and other complications considered likely to affect micturition</p> <p>Total number of participants randomly assigned: 46</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 23 age (years): 68.9 ± 5.6 prostate volume (mL): 35.0 ± 18.4 PSA (ng/mL): 2.5 ± 3.4 IPSS: 19.3 ± 4.9 Qmax (mL/s): 7.2 ± 2.9 <p>Group B (Tamsulosin)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 23 age (years): 70.0 ± 6.8 prostate volume (mL): 36.1 ± 15.5 PSA (ng/mL): 3.5 ± 3.7 IPSS: 21.1 ± 6.8 Qmax (mL/s): 7.6 ± 3.0
Interventions	<p>Run-in period: none</p> <p>Group A: silodosin 4 mg twice daily</p> <p>Group B: tamsulosin 0.2 mg once daily</p> <p>Duration: 3 months (before cross-over)/1 month wash-out/3 months (after cross-over)/total 7 months</p>
Outcomes	<ul style="list-style-type: none"> IPSS QoL index Qmax PVR <p>How measured: IPSS questionnaire and transabdominal US (PVR)</p> <p>Time points measured: before and after treatment (not reported in method)</p> <p>Time points reported: before and after treatment (1 months, 3 months, 4 months, and 7 months)</p> <p>Safety outcomes</p> <p>How measured: adverse events</p> <p>Time points measured: not reported</p> <p>Time points reported: not reported</p> <p>Subgroup: none</p>

Yokoyama 2012 (Continued)

Funding sources	None	
Declarations of interest	None	
Notes	Language of publication: English One month wash-out period between cross-over Data (IPSS, QoL, treatment withdrawal for any reason, method of random sequence generation, allocation concealment, and blinding) were given by contact with study author	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement: study author reply "random number table"
Allocation concealment (selection bias)	Unclear risk	Judgement: study author reply "sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: study author reply "participants were blinded"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Judgement: study author reply "participants were blinded"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 5/46 (10.9%) participants were not included in the analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: not available (cross-over trial)
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis

Yokoyama 2012 (Continued)

Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: prespecified outcomes are well described and data were given by study author, but protocol was not published (study author confirmed via email)
Other bias	Low risk	Judgement: not detected

Yu 2011

Methods	<p>Study design: parallel, randomized, double-blinded</p> <p>Setting/Country: 9 medical centers/Taiwan</p> <p>Dates when study was conducted: July 2007-September 2008</p>
Participants	<p>Inclusion criteria: men aged ≥ 40 years with an IPSS of ≥ 13, a health-related QoL score of ≥ 3, a prostate volume of ≥ 20 mL, and a Qmax of < 15 mL/s with a voided volume of ≥ 100 mL</p> <p>Exclusion criteria: men with a history of previous prostate surgery, prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, active urinary tract infection, a PVR of > 250 mL, exposure to sex hormone within 3 months prior to the wash-out period, renal dysfunction (serum creatinine of > 2.0 mg/dL), a history of severe liver impairment, severe cardiovascular diseases, severe hypotension, and known hypersensitivity or history of active substance abuse (including alcohol) within the past 2 years</p> <p>Total number of participants randomly assigned: 209</p> <p>Group A (Silodosin)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 105 age (years): 67.5 ± 9.3 prostate volume (mL): 44.8 ± 24.2 PSA (ng/mL): not reported IPSS: 19.3 ± 4.5 Qmax (mL/s): 10.3 ± 2.8 <p>Group B (Tamsulosin)</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 104 age (years): 65.0 ± 8.8 prostate volume (mL): 38.2 ± 16.7 PSA (ng/mL): not reported IPSS: 19.8 ± 4.5 Qmax (mL/s): 10.6 ± 2.8
Interventions	<p>Run-in period: 7-day wash-out and 7-day observation periods</p> <p>Group A: silodosin 4 mg twice daily</p> <p>Group B: tamsulosin 0.2 mg in the morning and one placebo capsule in the evening</p> <p>Duration: 12 weeks</p>
Outcomes	Primary outcome

Yu 2011 (Continued)

- change in the IPSS from baseline
- participants who achieved 25% reduction in the IPSS from baseline

How measured: IPSS questionnaire

Time points measured: 0 (initiation of treatment), 2, 4, 8, and 12 weeks

Time points reported: 0 (initiation of treatment), 2, 4, 8, and 12 weeks in figure

Secondary outcome

- Qmax
- health-related QoL from baseline
- changes in IPSS subscores (voiding and storage symptom scores)

How measured: uroflowmetry, IPSS questionnaire

Time points measured: 0, 4 and 12 weeks/0 (initiation of treatment), 2, 4, 8, and 12 weeks

Time points reported: 0 and 12 weeks

Safety outcomes

How measured: all adverse events/BP/pulse rate/laboratory tests

Time points measured: 0 (initiation of treatment), 2, 4, 8, and 12 weeks/0, 4 and 12 weeks/follow-up visits

Time points reported: 0 and 12 weeks/cumulative results from follow-up visits (adverse events)

Subgroup: none

Funding sources	Synmosa pharmaceutical company
Declarations of interest	All authors were study investigators for Synmosa
Notes	Language of publication: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement: no information given
Allocation concealment (selection bias)	Unclear risk	Judgement: no information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both investigators and patients were 'blinded' to treatment"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "both investigators and patients were 'blinded' to treatment"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement: objective outcomes are not likely affected by lack of blinding

Yu 2011 (Continued)

Incomplete outcome data (attrition bias) Urologic symptom scores/ QoL	Unclear risk	Judgement: 18/105 (17.1%), 21/104 (20.2%) participants who were randomized in silodosin, tamsulosin group were not included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Judgement: all participants who were randomized in each group were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) AUR/ surgical intervention	Unclear risk	Judgement: no information given
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Judgement: 18/105 (17.1%), 21/104 (20.2%) participants who were randomized in silodosin, tamsulosin group were not included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Judgement: 18/105 (17.1%), 21/104 (20.2%) participants who were randomized in silodosin, tamsulosin group were not included in analysis
Selective reporting (reporting bias)	Unclear risk	Judgement: protocol was published, but protocol was not found due to the absence of protocol number
Other bias	High risk	Judgement: serious baseline imbalance in age, IPSS, prostate volume, health-related QoL, Qmax in as treated analysis. Two weeks' observation run-in period

5-ARIs: 5-alpha reductase inhibitors; AUR: acute urinary retention; BP: blood pressure; BPH: benign prostatic hyperplasia; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; OABSS: Overactive Bladder Symptom Score; PSA: prostate-specific antigen; PVR: postvoid residual; Qmax; maximum flow rate; QoL: quality of life; US: ultrasound

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abramowicz 2009	Review
Alcántara Montero 2016	Review
Araki 2013	Wrong study design (non randomized trial)
Boeri 2016	Wrong study design (study design not described, silodosin versus silodosin plus <i>Serenoa repens</i>)
Cakiroglu 2016	Wrong comparator (silodosin versus transurethral incision of prostate)
Chapple 2009	Wrong study design (integrated safety analysis)

Study	Reason for exclusion
Curran 2011	Review
JPRN-UMIN000007917	Wrong comparator (silodosin 4 mg once daily versus silodosin 4 mg twice daily)
Kawabe 2006b	Wrong study design (non randomized study)
Kobayashi 2008	Wrong outcome (semen parameters)
Kobayashi 2009	Wrong outcome (semen parameters)
Manjunatha 2016b	Wrong outcome (cost effectiveness)
Matsukawa 2012	Wrong comparator (silodosin versus silodosin and propiverine)
Matsukawa 2017	Wrong comparator (silodosin and dutasteride versus dutasteride)
Michel 2011	Wrong study population (participants with ≥ 2 voids per night)
Montorsi 2010	Review
Montorsi 2013	Review
Prescrire Int 2011	Review (medical article)
Prescrire Int 2012	Review (medical article)
Roehrborn 2009	Wrong study population (participants with retrograde ejaculation as adverse event)
Yoshida 2017	Wrong comparator (silodosin versus phosphodiesterase 5 inhibitor)
Yoshihisa 2012	Wrong comparator (silodosin versus silodosin and propiverine)
Zhou 2011	Wrong outcome (pharmacokinetics and adverse events (not available))

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

[CTRI/2010/091/000526](#)

Methods	Randomized, parallel-group, active, controlled trial
Participants	Inclusion criteria <ul style="list-style-type: none"> Ages: > 45 years and < 80 years Genders eligible for study: male only Men in good general health and ≥ 50 years, with symptoms of moderate-severe BPH A mean symptoms score of ≥ 8 (symptoms of BPH assessed as per American Urological Association Symptom Index, which assesses the occurrence of seven symptoms characteristic of BPH during the preceding week, each scored on a scale from 0 (absent) to 5 (severe)). Mean Qmax of ≤ 15 mL/s and ≤ 4 mL/s, with a minimal voided volume of 125 mL, and a mean PVR of < 300 mL PSA values of > 4 ng/mL Renal function defined as a serum creatinine level of < 2.0 mg/dL and creatinine clearance of > 20 mL/min by Cockcroft and Gault formula

CTRI/2010/091/000526 (Continued)

Interventions	Group A: silodosin capsule 8 mg Group B: tamsulosin ER capsules 0.4 mg Duration: 12 weeks
Outcomes	<ul style="list-style-type: none"> • change in baseline score on the American Urological Association Symptom Index • change in baseline urine flow rate • change in PSA • safety and tolerability
Notes	Funding source: MSN Laboratories Ltd Publication status: CTRI/2010/091/000526 (final publication status has not been clarified)

Devana 2014

Methods	Open-label, parallel study
Participants	Inclusion criteria: men with symptomatic BPH aged 50-80 years, with IPSS > 8 or QoL score > 2 Exclusion criteria: not reported
Interventions	Group A: silodosin 8 mg/d Group B: tamsulosin 0.4 mg/d Group C: alfuzosin 10 mg/d Duration: 1 month
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL scores • Qmax • PVR • side effects
Notes	Publication status: abstract (final publication status has not been clarified)

Jha 2015

Methods	Parallel, randomized study
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Group A: silodosin 8 mg daily at night Group B: tamsulosin 0.4 mg daily at night Duration: 6 months
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL

Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Jha 2015 (Continued)

- digital rectal exam
- PSA
- Qmax
- PVR
- side effects

Notes	Publication status: abstract (final publication status has not been clarified)
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JPRN-UMIN000003125

Methods	Open-label, parallel, randomized study
Participants	<p>Inclusion criteria: male patients with newly diagnosed LUTS according to the treatment algorithm of the Clinical Practice Guidelines for male LUTS</p> <p>Exclusion criteria: men who meet any of the following criteria are excluded:</p> <ul style="list-style-type: none"> • taking anticholinergic agents, antidepressants, or antianxiety agents • a history of urinary retention, urinary tract infections, macroscopic hematuria, lower urinary tract surgery, radiotherapy for the pelvic organs, or neurologic disease • pyuria, renal impairment, calculus bladder, or urine cytology positive • elevated PSA levels (≥ 4.0 ng/mL) • 9th CLSS score ≥ 2 • not willing to receive drug treatment • cannot answer the questionnaire by themselves • classified as ineligible by the investigator
Interventions	<p>Group A: silodosin 8 mg daily</p> <p>Group B: tamsulosin 0.2 mg daily</p> <p>Duration: not reported</p>
Outcomes	<ul style="list-style-type: none"> • IPSS • Overactive Bladder Symptom Score • uroflowmetry • PVR • prostate volume
Notes	<p>Funding source: none</p> <p>Publication status: JPRN-UMIN000003125 (final publication status has not been clarified)</p>

JPRN-UMIN000005151

Methods	Parallel, randomized study
Participants	<p>Inclusion criteria</p> <p>Men aged ≥ 50 years with previously-untreated BPH with total IPSS ≥ 8 and QoL score ≥ 2</p>
Interventions	Group A: silodosin 4 mg twice daily

JPRN-UMIN000005151 (Continued)

Group B: tamsulosin hydrochloride 0.2 mg daily

Duration: not reported

Outcomes	<ul style="list-style-type: none"> • IPSS and QoL score • uroflowmetry • PVR • prostate volume • Japanese-Gastrointestinal symptom Rating Scale • Bristol Stool Form • safety (adverse events) • rate of discontinuation
Notes	<p>Funding source: none</p> <p>Publication status: JPRN-UMIN000005151 (final publication status has not been clarified)</p>

JPRN-UMIN000008538

Methods	Parallel, randomized study
Participants	<p>Inclusion criteria</p> <p>Men aged 50-90 years</p> <p>1) a total IPSS of ≥ 8</p> <p>2) Qmax of ≤ 15 mL/s as evaluated by uroflowmetry</p> <p>3) prostate volume of ≥ 15 mL as measured by prostatic US</p>
Interventions	<p>Group A: silodosin</p> <p>Group B: tamsulosin</p> <p>Duration: not reported</p>
Outcomes	<ul style="list-style-type: none"> • changes in IPSS • uroflowmetry • bladder diary
Notes	<p>Funding source: Dokkyo Medical University</p> <p>Publication status: JPRN-UMIN000008538 (final publication status has not been clarified)</p>

JPRN-UMIN000011556

Methods	Parallel, randomized study
Participants	<p>Inclusion criteria</p> <p>Men aged ≥ 50 years</p> <ul style="list-style-type: none"> • Participant must have urinary symptoms associated with BPH • Participant must give written informed consent

JPRN-UMIN000011556 (Continued)

- Participant must satisfy the following conditions during screening conducted at the start of the treatment period (Day 0): the total IPSS voiding symptom score is ≥ 8 , the QoL score is ≥ 2 , prostate volume is ≥ 20 mL, Qmax is ≤ 15 mL/s, and PVR is ≤ 100 mL
- Participant must not use prohibited concomitant drugs except at least 2 weeks before the start of the treatment period (Day 0), or the subject must be able to undergo a drug wash-out for at least 2 weeks before the start of the treatment period
- Participant must be an outpatient who can fill in the questionnaire
- Participant must be ≥ 65 years at the time of signing the informed consent

Interventions	<p>Group A: silodosin 4 mg, once daily after breakfast</p> <p>Group B: tamsulosin 0.2 mg, once daily after breakfast</p> <p>Duration: not reported</p>
Outcomes	<ul style="list-style-type: none"> • IPSS total score and subscores • QoL score • Overactive bladder symptom score • urodynamic parameters • blood pressure • adverse events and adverse drug reactions
Notes	<p>Funding source: Kissei Pharmaceutical Co., Ltd</p> <p>Publication status: JPRN-UMIN000011556 (final publication status has not been clarified)</p>

Mandal 2013

Methods	Open-label, parallel study
Participants	<p>Inclusion criteria: men with symptomatic BPH aged 50-80 years with IPSS > 8 or QoL score > 2</p> <p>Exclusion criteria: other causes of bladder outlet obstruction, prostate and bladder malignancy, renal failure, hepatic failure and prior history of prostatectomy</p>
Interventions	<p>Group A: silodosin 8 mg/d</p> <p>Group B: tamsulosin 0.4 mg/d</p> <p>Group C: alfuzosin 10 mg/d</p> <p>Duration: 1 month</p>
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL • Qmax • average urinary flow rate • PVR • side effects
Notes	Publication status: abstract (final publication status has not been clarified)

Manohar 2014

Methods	Parallel, randomized study
Participants	Inclusion criteria: patients of LUTS in BPH Exclusion criteria: not reported
Interventions	Group A: silodosin 8 mg once/d Group B: tamsulosin 0.4 mg once/d Group C: alfuzosin 10 mg once/d Duration: 12 weeks
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL • Qmax • PVR • safety profile
Notes	Publication status: abstract (final publication status has not been clarified)

Miyamae 2011

Methods	Parallel, randomized study
Participants	Inclusion criteria: men with untreated BPH <ul style="list-style-type: none"> • gave their informed consent to participate in this study • outpatients aged ≥ 50 years • total IPSS of ≥ 8 and QoL score of ≥ 3 • never been treated with an alpha-1-blocker or had not received an alpha-1-blocker for at least 4 weeks • judged by attending physicians to be eligible for participation in the study Exclusion criteria: not reported
Interventions	Group A: silodosin 4 mg twice daily Group B: tamsulosin 0.2 mg once daily Duration: 1 week
Outcomes	<ul style="list-style-type: none"> • IPSS • Overactive Bladder Symptom Score • QoL rating scale • side effects
Notes	Publication status: abstract (final publication status has not been clarified)

NCT01222650

Methods	Parallel, randomized, double-blind, placebo-controlled study
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NCT01222650 (Continued)

Participants	<p>Inclusion criteria: men with BPH and LUTS</p> <p>Exclusion criteria: history of prostatectomy, intrapelvic radiation therapy, thermotherapy of prostate or prostatic hyperthermia, prostate cancer or suspected prostate cancer, any clinically relevant cardiovascular, hepatic or renal disorder</p>
Interventions	<p>Group A: not reported</p> <p>Group B: not reported</p> <p>Duration: 12 weeks</p>
Outcomes	<ul style="list-style-type: none"> • change in IPSS total score from baseline • change in IPSS subscore • QoL score • Qmax from baseline
Notes	<p>Funding source: Kissei Pharmaceutical Co., Ltd</p> <p>Publication status: NCT01222650 (final publication status has not been clarified)</p>

Pawar 2015

Methods	Parallel, randomized study
Participants	<p>Inclusion criteria: men > 45 years with symptomatic BPH (increased daytime frequency, urgency and nocturia and or voiding symptoms (hesitancy, incomplete voiding, impaired stream or interruption of stream), increased daytime micturition, nocturia > 2, maximum flow rate < 15 mL/sec with a voided volume of ≥ 150 mL, PVR < 100 mL by abdominal US, IPSS > 13 points, international prostatic symptom bother score > 3 points</p> <p>Exclusion criteria: not reported</p>
Interventions	<p>Group A: silodosin 8 mg once daily</p> <p>Group B: tamsulosin 0.2 mg once daily</p> <p>Duration: 12 weeks</p>
Outcomes	<ul style="list-style-type: none"> • clinical determination of IPSS, Qmax index • Qmax (mL/s) • time to maximum flow rate • average flow rate • average flow time • PVR • prostate size by transabdominal ultrasonographically • adverse events
Notes	Publication status: abstract (final publication status has not been clarified)

BPH: benign prostatic hyperplasia; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; PSA: prostate specific antigen; PVR: postvoid residual; Qmax; maximum flow rate; QoL: quality of life; US: ultrasound

Characteristics of ongoing studies [ordered by study ID]

CTRI/2013/10/004112

Trial name or title	A study to find out the medication which offers maximum health benefits with minimum spending by the patient among the three commonly used medications in the treatment of benign prostatic hyperplasia, a disease in aging men which results in bothersome urinary problems
Methods	Randomized, parallel group trial
Participants	Inclusion criteria <ul style="list-style-type: none"> • Men $\geq$ 45 years with BPH and associated LUTS • IPSS $\geq$ 8 • QoL score $\geq$ 3 • Qmax < 15 mL/s but > 4 mL/s with a voided volume of >100 mL • Willingness to give written informed consent and to comply with the study procedure, and available for regular follow-up
Interventions	Group A: silodosin oral, 8 mg once daily Group B: tamsulosin oral, 0.4 mg once daily Group C: alfuzosin oral, 10 mg once daily Duration: 12 weeks
Outcomes	Treatment success is defined as $\geq$ 30% improvement in IPSS from baseline and its maintenance over the study period
Starting date	September 2013
Contact information	manjunatha5ramaiah@gmail.com
Notes	Funding source: none

JPRN-UMIN000003609

Trial name or title	The effects of selective alpha-1-adrenergic receptor antagonists in patients with lower urinary tract symptoms caused by benign prostatic hyperplasia who failed to obtain sufficient efficacy by previous alpha-1-blockades. A comparison of naftopidil or silodosin
Methods	Parallel, randomized
Participants	Inclusion criteria <p>Men with LUTS caused by BPH who failed to obtain sufficient efficacy by naftopidil 50 mg and with IPSS of $\geq$ 9, a QoL score of $\geq$ 2, a prostate volume of $\geq$ 20 mL are eligible for enrolment</p>
Interventions	Group A: silodosin 8 mg Group B: naftopidil 75 mg Duration: not reported
Outcomes	<ul style="list-style-type: none"> • IPSS • QoL score • blood pressure • uroflowmetry

JPRN-UMIN000003609 (Continued)

Starting date	May 2010
Contact information	Email address was not given
Notes	Funding source: none

BPH: benign prostatic hyperplasia; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; Qmax; maximum flow rate; QoL: quality of life

DATA AND ANALYSES

Comparison 1. Silodosin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urologic symptom scores (short term)	3	1743	Mean Difference (IV, Random, 95% CI)	-2.65 [-3.23, -2.08]
2 Quality of life (short term)	2	820	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.71, -0.13]
3 Treatment withdrawal due to any reason (short term)	3	1703	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.70, 1.66]
4 Treatment withdrawal due to adverse events (short term)	4	1967	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.41, 3.72]
5 Cardiovascular adverse events (short term)	4	1967	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.67, 2.45]
6 Sexual adverse events (short term)	4	1967	Risk Ratio (M-H, Random, 95% CI)	26.07 [12.36, 54.97]

Analysis 1.1. Comparison 1 Silodosin versus placebo, Outcome 1 Urologic symptom scores (short term).

Analysis 1.2. Comparison 1 Silodosin versus placebo, Outcome 2 Quality of life (short term).

Analysis 1.3. Comparison 1 Silodosin versus placebo, Outcome 3 Treatment withdrawal due to any reason (short term).

Analysis 1.4. Comparison 1 Silodosin versus placebo, Outcome 4 Treatment withdrawal due to adverse events (short term).

Analysis 1.5. Comparison 1 Silodosin versus placebo, Outcome 5 Cardiovascular adverse events (short term).

Analysis 1.6. Comparison 1 Silodosin versus placebo, Outcome 6 Sexual adverse events (short term).

Comparison 2. Silodosin versus tamsulosin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urologic symptom scores (short term)	10	1708	Mean Difference (IV, Random, 95% CI)	-0.04 [-1.31, 1.24]
2 Quality of life (short term)	10	1707	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.53, 0.22]
3 Treatment withdrawal due to any reason (short term)	10	1573	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.62, 1.69]
4 Treatment withdrawal due to adverse events (short term)	9	1572	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.12, 3.44]
5 Cardiovascular adverse events (short term)	11	1955	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Sexual adverse events (short term)	10	1849	Risk Ratio (M-H, Random, 95% CI)	6.05 [3.55, 10.31]

Analysis 2.1. Comparison 2 Silodosin versus tamsulosin, Outcome 1 Urologic symptom scores (short term).

Analysis 2.2. Comparison 2 Silodosin versus tamsulosin, Outcome 2 Quality of life (short term).

Analysis 2.3. Comparison 2 Silodosin versus tamsulosin, Outcome 3 Treatment withdrawal due to any reason (short term).

Analysis 2.4. Comparison 2 Silodosin versus tamsulosin, Outcome 4 Treatment withdrawal due to adverse events (short term).

Analysis 2.5. Comparison 2 Silodosin versus tamsulosin, Outcome 5 Cardiovascular adverse events (short term).

Analysis 2.6. Comparison 2 Silodosin versus tamsulosin, Outcome 6 Sexual adverse events (short term).

Comparison 3. Silodosin versus naftopidil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urologic symptom scores (short term)	5	652	Mean Difference (IV, Random, 95% CI)	-0.85 [-2.57, 0.87]
2 Quality of life (short term)	5	652	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.60, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Treatment withdrawal due to any reason (short term)	4	659	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.81, 1.93]
4 Treatment withdrawal due to adverse events (short term)	5	738	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.66, 2.89]
5 Cardiovascular adverse events (short term)	5	808	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.41, 2.56]
6 Sexual adverse events (short term)	4	405	Risk Ratio (M-H, Random, 95% CI)	5.93 [2.16, 16.29]

Analysis 3.1. Comparison 3 Silodosin versus naftopidil, Outcome 1 Urologic symptom scores (short term).

Analysis 3.2. Comparison 3 Silodosin versus naftopidil, Outcome 2 Quality of life (short term).

Analysis 3.3. Comparison 3 Silodosin versus naftopidil, Outcome 3 Treatment withdrawal due to any reason (short term).

Analysis 3.4. Comparison 3 Silodosin versus naftopidil, Outcome 4 Treatment withdrawal due to adverse events (short term).

Analysis 3.5. Comparison 3 Silodosin versus naftopidil, Outcome 5 Cardiovascular adverse events (short term).

Analysis 3.6. Comparison 3 Silodosin versus naftopidil, Outcome 6 Sexual adverse events (short term).

Comparison 4. Silodosin versus alfuzosin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urologic symptom scores (short term)	1	60	Mean Difference (IV, Random, 95% CI)	3.83 [0.12, 7.54]
2 Quality of life (short term)	1	60	Mean Difference (IV, Random, 95% CI)	0.14 [-0.46, 0.74]
3 Cardiovascular adverse events (short term)	1	60	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.36, 1.24]
4 Sexual adverse events (short term)	1	95	Risk Ratio (M-H, Random, 95% CI)	37.21 [5.32, 260.07]

Analysis 4.1. Comparison 4 Silodosin versus alfuzosin, Outcome 1 Urologic symptom scores (short term).

Analysis 4.2. Comparison 4 Silodosin versus alfuzosin, Outcome 2 Quality of life (short term).

Analysis 4.3. Comparison 4 Silodosin versus alfuzosin, Outcome 3 Cardiovascular adverse events (short term).

Analysis 4.4. Comparison 4 Silodosin versus alfuzosin, Outcome 4 Sexual adverse events (short term).

ADDITIONAL TABLES

Table 1. Baseline characteristics of included studies

Study name	Trial period (year to year)	Country	Setting	Description of participants	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)	Age	Prostate volume	IPSS
Chapple 2011	2006-2007	Europe	72 hospital clinics and in-patient units in 11 countries	Men ≥ 50 years with LUTS (defined by a stable IPSS total score ≥ 13 points), bladder outlet obstruction (defined by a Qmax between 4 and 15 mL/s, with a minimum voided volume of ≥ 125 mL)	Silodosin 8 mg once daily	12 weeks	65.8 ± 7.70	NR	19.1 ± 4.2
					Tamsulosin 0.4 mg once daily		65.9 ± 7.41		18.9 ± 4.3
					Placebo once daily		66.0 ± 7.37		19.3 ± 4.3
Jung 2012	NR	South Korea	NR	Sexually active men with BPH	Silodosin 8 mg once daily	4 weeks	NR	NR	NR
					Tamsulosin 0.2 mg once daily				
					Alfuzosin 10 mg once daily				
Kawabe 2006a	NR	Japan	88 centers/out-patient	Men ≥ 50 years with LUTS (IPSS of ≥ 8, an associated QoL score of ≥ 3) and prostate volume of ≥ 20 mL	Silodosin 4 mg twice daily	12 weeks	65.4 ± 7.0	36.0 ± 16.9	17.1 ± 5.7
					Tamsulosin 0.2 mg once daily		65.6 ± 7.0	35.7 ± 14.4	17.0 ± 5.7
					Placebo twice daily		65.0 ± 6.9	35.2 ± 16.0	17.1 ± 6.1
Manjunatha 2016a	2013-2014	India	Tertiary care hospital	Men ≥ 45 years with symptomatic BPH with LUTS (IPSS of ≥ 8, QoL of ≥ 3, and Qmax of < 15 mL/s, but > 4 mL/s with a voided volume of > 100 mL)	Silodosin 8 mg once daily	12 weeks	64.00 ± 11.14	40.57 ± 16.45	15.93 ± 6.03
					Tamsulosin 0.4 mg once daily		63.60 ± 9.05	40.33 ± 21.55	21.63 ± 7.63
					Alfuzosin 10 mg once daily		63.43 ± 8.91	44.43 ± 27.72	19.2 ± 9.6

Table 1. Baseline characteristics of included studies (Continued)

Marks 2009	2005-2006	USA	Multicen- ter	Men ≥ 50 years with IPSS ≥ 13, Qmax 4 mL/s-15 mL/s and a PVR < 250 mL	Silodosin 8 mg once dai- ly	12 weeks	64.6 ± 8.1	NR	21.3 ± 5.1
					Placebo once daily		64.7 ± 8.1		21.3 ± 4.9
Masuda 2012	2009-2011	Japan	NR	Men ≥ 50 years with prostate estimated volume of > 20 mL, IPSS ≥ 8, QoL score ≥ 3 points	Silodosin 2 mg-4 mg twice/d for 2 weeks, fol- lowed by 4 mg twice/d for 4 weeks	6 weeks (before cross- over)/total 12 weeks	66.5 ± 5.6	38.8 ± 13.1	18.6 ± 5.5
					Naftopidil 50 mg-75 mg once/d for 2 weeks, fol- lowed by 75 mg once/d for 4 weeks		68.5 ± 5.7	45.7 ± 17.8	17.6 ± 5.0
Mat- sukawa 2016	2012-2013	Japan	52 urolo- gists par- ticipat- ed at a to- tal of 44 investi- gational sites/out- patients	Men with LUTS (IPSS ≥ 8, IPSS QoL score 3) and prostate vol- ume ≥ 20 mL	Silodosin 4 mg/d for 4 weeks, followed by 8 mg/d for 8 weeks	12 weeks	70.6 ± 7.8	39.6 ± 16.7	18.8 ± 6.2
					Naftopidil 50 mg/d for 4 weeks, followed by 75 mg/d for 8 weeks		70.3 ± 7.8	38.6 ± 14.8	18.9 ± 6.1
Miyakita 2010	2006-2007	Japan	Multicen- ter	Men with IPSS ≥ 8 points; QoL score ≥ 3 points; prostate vol- ume measured by ultrasono- graphic method ≥ 20 mL; void volume ≥ 100 mL; and maximal urinary flow rate (Qmax) < 15 mL/s	Silodosin 4 mg twice dai- ly	4 weeks (before cross- over)/total 8 weeks	68.2 ± 8.6	41.3 ± 25.3	16.6 ± 5.2
					Tamsulosin 0.2 mg once daily		70.1 ± 8.9	37.8 ± 16.3	18.2 ± 5.8
Natarajan 2015	2013-2015	India	Tertiary hospital	Men > 50 years with bother- some LUTS from BPH and IPSS > 7	Silodosin 8 mg once dai- ly	12 weeks	61 - 62	NR	NR
					Tamsulosin 0.4 mg once daily				
NCT00793819	2009	NR	NR	Men ≥ 50 years, with symptoms of moderate-severe BPH and nocturia (≥ 2 episodes/night)	Silodosin 8 mg daily	12 weeks	64.6 ± 8.03	NR	NR
					Placebo once daily		64.2 ± 8.92		

Table 1. Baseline characteristics of included studies (Continued)

Pande 2014	2012-2013	India	Tertiary care hospital/ out-patient	Men > 50 years with bothersome LUTS from BPH and IPSS > 7	Silodosin 8 mg once daily	12 weeks	61.4 ± 7.88	42.0 ± 19.96	18.4 ± 3.32
					Tamsulosin 0.4 mg once daily		62.6 ± 7.55	35.6 ± 9.56	18.4 ± 3.94
Shi-rakawa 2013	2007-2011	Japan	Kobe University School or other collaborating institutions	Men with LUTS (total IPSS ≥ 8, QoL index ≥ 3) and prostate volume ≥ 20 mL	Silodosin 4 mg twice daily	8 weeks	70.98 ± 6.69	38.24 ± 12.94	17.53 ± 5.4
					Naftopidil 50 mg once daily		70.50 ± 6.58	39.39 ± 25.96	17.56 ± 6.7
Takeshita 2016	2011-2014	Japan	Four community-based hospitals	Men aged ≥ 50 years with LUTS/ BPH, an IPSS of ≥ 8, QoL score of ≥ 3, and ultrasound-estimated prostatic volume of ≥ 20 mL	Silodosin 4 mg once daily	4 weeks (before cross-over)/total 8 weeks	69.6 ± 5.4	38.7 ± 11.6	17.1 ± 7.3
					Tamsulosin 0.2 mg once daily		69.4 ± 7.0	47.3 ± 30.4	15.2 ± 7.0
Watanabe 2011	2008-2009	Japan	Three institutions	Men with LUTS associated with BPH and had an IPSS ≥ 8 and an IPSS-QoL score ≥ 2	Silodosin 4 mg twice daily	4 weeks (before cross-over)/total 8 weeks	69.3 ± 8.3	36.6 ± 18.3	16.4 ± 5.0
					Tamsulosin 0.2 mg once daily		69.9 ± 8.4	35.1 ± 13.0	18.1 ± 6.2
Yam-aguchi 2013	2007-2010	Japan	Nihon University School of Medicine	Men with BPH, ≥ 50 years with significant LUTS (IPSS ≥ 8, QoL score ≥ 3)	Silodosin 8 mg/ day	12 weeks	69.3 ± 7.8	33.2 ± 21.2	16.9 ± 5.5
					Naftopidil 75 mg/ day		70.0 ± 7.0	39.5 ± 18.0	18.9 ± 7.0
Yaman-ishi 2011	NR	NR	NR	Men with LUTS (IPSS total score ≥ 8, Qmax < 15 mL/s) and prostate volume > 20 mL	Silodosin 4 mg twice daily	12 months	71.3 ± 8.2	42.0 ± 23.7	18.8 ± 7.3
					Tamsulosin 0.2 - 0.4 mg daily		72.2 ± 7.6	41.2 ± 23.0	17.8 ± 6.4
Yokoya-ma 2011	NR	Japan	Kawasaki Medical School	Men aged 50--80 years and with IPSS ≥ 8	Silodosin 4 mg twice daily	12 weeks	70.2 ± 0.9	33.3 ± 2.3	18.7 ± 0.7
					Tamsulosin 0.2 mg once daily		71.5 ± 1.1	32.5 ± 2.0	18.0 ± 1.1

Table 1. Baseline characteristics of included studies (Continued)

					Naftopidil 50 mg once daily		69.1 ± 1.2	35.0 ± 3.1	17.4 ± 0.8
Yokoyama 2012	2008-2010	Japan	Single center	Men aged 50 years who had a total IPSS ≥ 8 and a QoL index ≥ 3	Silodosin 4 mg twice daily	3 months (before cross-over)/1 month wash-out/3 months (after cross-over)/total 7 months	68.9 ± 5.6	35.0 ± 18.4	19.3 ± 4.9
					Tamsulosin 0.2 mg once daily		70.0 ± 6.8	36.1 ± 15.5	21.1 ± 6.8
Yu 2011	2007-2008	Taiwan	Nine medical centers	Men aged ≥ 40 years with an IPSS of ≥ 13 and prostate volume of ≥ 20 mL	Silodosin 4 mg twice daily	12 weeks	67.5 ± 9.3	44.8 ± 24.2	19.3 ± 4.5
					Tamsulosin 0.2 mg and one placebo		65.0 ± 8.8	38.2 ± 16.7	19.8 ± 4.5

BPH: benign prostatic hyperplasia; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; NR: not reported; PVR: postvoid residual; Qmax: maximum flow rate; QoL: quality of life

Table 2. Participants in included studies

Study name	Intervention(s) and comparator(s)	Screened/eligible (N)	randomized (N)	Analysed (N)	Finishing trial (N (%))
Chapple 2011	Silodosin 8 mg	1228/955	381	346	356 (93.4)
	Tamsulosin 0.4 mg		384	347	364 (94.7)
	Placebo		190	168	172 (90.5)
	Total		955	861	892 (93.4)
Jung 2012	Silodosin 8 mg	NR/138	48	48	48 (100.0)
	Tamsulosin 0.2 mg		43	43	43 (100.0)
	Alfuzosin 10 mg		47	47	47 (100.0)
	Total		138	138	138 (100.0)
Kawabe 2006a	Silodosin 8 mg	NR/457	176	175	175 (99.4)
	Tamsulosin 0.2 mg		192	192	192 (100.0)
	Placebo		89	89	89 (100.0)
	Total		457	456	456 (99.7)
Manjunatha 2016a	Silodosin 8 mg	NR/90	30	30	30 (100.0)
	Tamsulosin 0.4 mg		30	30	30 (100.0)
	Alfuzosin 10 mg		30	30	30 (100.0)
	Total		90	90	90 (100.0)
Marks 2009	Silodosin 8 mg	2849/923	466	466	413 (88.6)
	Placebo		457	457	419 (91.6)
	Total		923	923	832 (90.1)
Masuda 2012	Silodosin 4 mg or 8 mg	NR/92	44	30/83 ^a	30 (68.1)
	Naftopidil 50 mg or 75 mg		48	34/79 ^a	34 (70.8)
	Total		92	64/162 ^a	64 (69.5)
Matsukawa 2016	Silodosin 4 mg followed by 8 mg	NR/350	175	157	157 (89.7)
	Naftopidil 50 mg followed by 75 mg		175	157	157 (89.7)
	Total		350	314	314 (89.7)

Table 2. Participants in included studies (Continued)

Miyakita 2010	Silodosin 8 mg	NR/97	46	34	34 (73.9)
	Tamsulosin 0.2 mg		51	31	31 (60.7)
	Total		97	65	65 (67.0)
Natarajan 2015	Silodosin 8 mg	NR/57	28	NR	NR
	Tamsulosin 0.4 mg		29	NR	NR
	Total		57	NR	NR
NCT00793819	Silodosin 8 mg	215/209	111	111	97 (87.3)
	Placebo		98	98	89 (90.8)
	Total		209	209	186 (88.9)
Pande 2014	Silodosin 8 mg	102/61	32	26	26 (81.2)
	Tamsulosin 0.4 mg		29	27	27 (93.1)
	Total		61	53	53 (86.8)
Shirakawa 2013	Silodosin 8 mg	NR/121	61	56/59 ^a	56 (91.8)
	Naftopidil 50 mg		60	56/57 ^a	56 (93.3)
	Total		121	112/116 ^a	112 (92.5)
Takeshita 2016	Silodosin 4 mg	NR/34	18	16	16 (88.8)
	Tamsulosin 0.2 mg		16	14	14 (87.5)
	Total		34	30	30 (88.2)
Watanabe 2011	Silodosin 4 mg	NR/102	51	42/88 ^a	42 (82.3)
	Tamsulosin 0.2 mg		51	42/91 ^a	42 (82.3)
	Total		102	84/179 ^a	42 (82.3)
Yamaguchi 2013	Silodosin 8 mg	109/109	58	53	53 (91.3)
	Naftopidil 75 mg		51	44	44 (86.2)
	Total		109	97	97 (88.9)
Yamanishi 2011	Silodosin 8 mg	NR/149	75	NR	NR
	Tamsulosin 0.2 - 0.4 mg		74	NR	NR
	Total		149	NR	NR
Yokoyama 2011	Silodosin 8 mg	136/136	45	41	41 (91.1)

Table 2. Participants in included studies (Continued)

	Tamsulosin 0.2 mg		45	39	39 (86.6)
	Naftopidil 50 mg		46	42	42 (91.3)
	Total		136	122	122 (89.7)
Yokoyama 2012	Silodosin 8 mg	NR/46	23	23	23 (100.0)
	Tamsulosin 0.2 mg		23	23	23 (100.0)
	Total		46	46	46 (100.0)
Yu 2011	Silodosin 8 mg	NR/209	105	87	87 (82.8)
	Tamsulosin 0.2 mg		104	83	83 (79.8)
	Total		209	170	170 (81.3)
Grand total	Interventions: silodosin		1955		1684 ^b
	Compartors: placebo		834		769 (92.2)
	Compartors: tamsulosin		1049		888 ^b
	Compartors: naftopidil		380		333 (87.6)
	Comparator: alfuzosin		77		77 (100.0)
	Overall		4295		3751 ^b

N: number; NR: not reported

^a Efficacy analysis/safety analysis.

^b The number of participants who finished trials were not reported in two included studies (Natarajan 2015; Yamanishi 2011).

APPENDICES

Appendix 1. Search strategies

Cochrane Library (via Wiley) search strategy

1. "Prostatic Hyperplasia" [Mesh]
2. (hyperplasia NEAR/3 prostat*):ti,ab,kw
3. "hyperplasia of the prostate":ti,ab,kw
4. "prostatic hyperplasia":ab,ti
5. (hypertrophy NEAR/3 prostat*):ti,ab,kw
6. (adenoma* NEAR/3 prostat*):ti,ab,kw
7. "lower urinary tract symptom" [Mesh]

(Continued)

8. "lower urinary tract": ti,ab,kw
9. LUTS: ti,ab,kw
10. "prostatism": ti,ab,kw
11. "prostatism"[Mesh]
12. "Urinary Bladder Neck Obstruction" [Mesh]
13. "bladder outlet obstruction": ti,ab,kw
14. (prostat* NEAR/3 enlarg*): ti,ab,kw
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. silodosin: ti,ab,kw
17. "KMD-3213": ti,ab,kw
18. 16 or 17

MEDLINE (via Pubmed) search strategy

1. "Prostatic Hyperplasia" [Mesh] or prostatic hyperplasia [TIAB]
2. "Lower Urinary Tract Symptoms" [Mesh] or lower urinary tract [TIAB] or LUTS [TIAB]
3. hyperplasia of the prostate [TIAB]
4. "Prostatic hypertrophy" [TIAB]
5. "Prostatic adenoma" [TIAB]
6. "Prostatism" [Mesh] or Prostatism [TIAB]
7. "Urinary Bladder Neck Obstruction" [Mesh] or "Urinary Bladder Neck Obstruction" [TIAB]
8. bladder outlet obstruction [TIAB]
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. silodosin [Supplementary Concept]
11. silodosin [TIAB]
12. KMD-3213 [TIAB]
13. rapaflo [TIAB]
14. urief [TIAB]
15. urorec [TIAB]
16. 10 or 11 or 12 or 13 or 14 or 15
17. randomized controlled trial [PT]
18. controlled clinical trial [PT]
19. randomized [TIAB]
20. placebo [TIAB]
21. drug therapy [Sh]
22. randomly [TIAB]

(Continued)

23. trial [TIAB]
24. groups [TIAB]
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 9 AND 16 AND 25
27. (animals [Mesh]) NOT (humans [Mesh] and animals [Mesh])
28. 26 NOT 27

EMBASE (via Elsevier) search strategy

1. 'prostate hypertrophy'/exp
2. (hyper* NEAR/3 prostat*):ab,ti
3. (adenoma* NEAR/3 prostat*):ab,ti
4. 'BPH' or 'BPO' or 'BPE':ab,ti
5. 'lower urinary tract symptom'/exp
6. 'lower urinary tract' or 'LUTS':ab,ti
7. 'prostatism':ab,ti
8. 'prostatism'/exp
9. 'bladder obstruction'/exp
10. ('bladder* NEAR/3 obstruct*') or 'BOO':ab,ti
11. (prostat* NEAR/3 (enlarg* or obstruct*)):ab,ti
12. ((urinary or urethra* or urination or LUT*) NEAR/3 (symptom* or complain*)):ab,ti
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 'silodosin'/exp
15. silodosin or 'KMD-3213' or kad3213 or rapaflo or silodyx or urief or urorec or Silofast or Thrupas:tw
16. '160970-54-7' or '160970-64-9' or '169107-04-4':rn
17. 14 or 15 or 16
18. random\$ or factorial\$ or crossover\$ or cross over\$ or 'cross-over\$' or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$:tw
19. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp
20. 18 or 19
21. 13 AND 17 AND 20
22. ('animals'/exp) NOT ('humans'/exp and 'animals'/exp)
23. 21 NOT 22

Scopus search strategy

1. TITLE-ABS-KEY (hyperplasia W/3 prostat*)
2. TITLE-ABS-KEY (hypertrophy W/3 prostat*)

(Continued)

3. TITLE-ABS-KEY (adenoma* W/3 prostat*)
4. TITLE-ABS-KEY (prostat* W/3 (enlarg* or obstruct*))
5. TITLE-ABS-KEY ((urinary OR urethra* OR urination OR lut*) W/3 (symptom* OR complain*))
6. TITLE-ABS-KEY (prostatism)
7. TITLE-ABS-KEY (bladder* W/3 obstruct*)
8. TITLE-ABS-KEY ("lower urinary tract")
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. TITLE-ABS-KEY (silodosin or 'KMD-3213' or rapaflo or silodyx or urief or urorec or Silofast or Thrupas)
11. CASREGNUMBER (160970-54-7 OR 160970-64-9 OR 169107-04-4)
12. 10 or 11
13. TITLE-ABS-KEY ("Double blind*" OR "Single Blind*" OR "Cross over stud*")
14. 9 AND 12 AND 13

Google Scholar search strategy

allintitle: ("Prostatic Hyperplasia" OR "prostate hypertrophy" OR "hyperplasia of the prostate" OR "lower urinary tract" OR "LUTS" OR prostatism OR "bladder obstruction" OR "bladder outlet obstruction") AND (silodosin OR KMD-3213 OR rapaflo OR Silodyx OR kad3213 OR urief OR urorec OR Silodal OR Rapolif OR Silofast OR Thrupas)

Web of Science search strategy

1. TS = (hyper* NEAR/3 prostat*) OR (adenoma* NEAR/3 prostat*) OR "BPH" OR "BPO" OR "BPE" OR "lower urinary tract" OR "luts" OR prostatism OR ("bladder NEAR/3 obstruct*") OR "BOO" OR (prostat* NEAR/3 (enlarg* or obstruct*)) OR ((urinary or urethra* or urination or LUT*) NEAR/3 (symptom* or complain*))
2. TS = (silodosin OR KMD-3213 OR rapaflo OR urief)
3. TS = "clinical trial*" OR "controlled trial*" OR "randomized controlled trial*" OR (single blind*) OR (double blind*)
4. 1 AND 2 AND 3

ClinicalTrials.gov

Basic search = ("Prostatic Hyperplasia" OR "prostate hypertrophy" OR "hyperplasia of the prostate" OR "lower urinary tract" OR "LUTS" OR prostatism OR "bladder obstruction" OR "bladder outlet obstruction") AND (silodosin OR KMD-3213 OR rapaflo OR urief OR Thrupas)

World Health Organization International Clinical Trials Registry Platform Search Portal

In the title = ("Prostatic Hyperplasia" OR "prostate hypertrophy" OR "hyperplasia of the prostate" OR "lower urinary tract" OR "LUTS" OR prostatism OR "bladder obstruction" OR "bladder outlet obstruction") AND In the intervention= (silodosin OR KMD-3213 OR rapaflo OR Silodyx OR urief OR urorec OR Silodal OR Thrupas)

Appendix 2. Survey of trial investigators providing information on included trials

	Date trial author contacted (first)	Date trial author provided data (latest)	Data trial author provided (short summary)
Chapple 2011	22 Jan 2017	2 Feb 2017	Unadjusted change from baseline in IPSS and QoL, mean and standard deviation of IPSS and QoL at endpoint (12 weeks), the number of participants with acute urinary retention and surgical intervention.
Jung 2012	18 Jan 2017	28 Feb 2017	Author reply: "Full text was not published".
Marks 2009	23 Jan 2017	23 Jan 2017	Author reply: "Pharmaceutics only have a data". We cannot contact study supporter in pharmaceutics due to wrong email address.
Pande 2014	24 Jan 2017	18 May 2017	Mean and standard deviation of IPSS and QoL at baseline and endpoint (12 weeks), the number of participants with acute urinary retention, surgical intervention, cardiovascular adverse events, and sexual adverse events.
Takeshita 2016	24 Oct 2017	3 Nov 2017	Change from baseline to 4 weeks (before cross-over) IPSS and QoL (mean and standard deviation). Treatment withdrawal and adverse events at 4 weeks (before cross-over). Method of random sequence generation and allocation concealment.
Yamaguchi 2013	27 Jan 2017	1 Feb 2017	Change from baseline in IPSS and QoL (mean and standard deviation), the number of participants with treatment withdrawal, acute urinary retention, surgical intervention, and cardiovascular adverse events. Method of random sequence generation and blinding.
Yamanishi 2011	27 Jan 2017	31 Jan 2017	Author reply: "Full text was not published".
Yokoyama 2011	30 Jan 2017	13 March 2017	Dates when study was conducted, study duration (intervention), exclusion criteria, conflicts of interest, mean and standard deviation of IPSS and QoL at baseline and endpoint (12 weeks), the number of participants with acute urinary retention and surgical intervention. Method of random sequence generation and blinding.
Yokoyama 2012	24 Oct 2017	29 Oct 2017	Total number of participants who were analyzed and finishing the trial at 3 months (before cross-over), change from baseline to 3 months (before cross-over) in IPSS and QoL (mean and standard deviation), Treatment withdrawal at 3 months (before cross-over). Method of random sequence generation and blinding. Presence of published protocol.

Footnotes

IPSS: International Prostate Symptom Score; QoL: quality of life

CONTRIBUTIONS OF AUTHORS

JH Jung (JHJ): conception and study design, drafting the protocol, searching for trials, study selection, extracting data, assessing risk of bias, performing data analysis, interpretation of data, and drafting the review.

J Kim (JK): drafting the protocol, searching for trials, study selection, extracting data, assessing risk of bias, performing data analysis, and drafting the review.

R MacDonald (RM): study design, drafting the protocol, providing clinical and methodological advices on the review, and final approval.

B Reddy (BR): providing clinical and methodological advice on the review, and drafting the review.

MH Kim (MHK): creating search strategies, drafting the protocol, and searching for trials.

P Dahm (PD): conception and study design, providing clinical and methodological advice on the review, and final approval.

DECLARATIONS OF INTEREST

JHJ: none known

JK: none known

RM: none known

BR: none known

MHK: none known

PD: PD serves as Co-ordinating Editor of Cochrane Urology. However, he was not involved in the editorial processing or decision-making for this review. Other editors of Cochrane Urology managed the editorial process, including final sign-off for this review.

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Internal sources

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External sources

- No sources of support provided, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol with differences as described here.

- Types of studies: we included parallel, randomized trials as well as cross-over designs. We revised the 'Types of studies' and 'Unit of analysis issues' section accordingly.
- Types of participants: we redefined the type of participants as adult men aged 40 years and over. Given that alpha-blockers are used to treat patients with all degrees of LUTS, we deleted the IPSS criterion under 'Types of participants'.
- Types of outcome measures: we renamed primary and secondary outcomes and added details in 'method and timing of outcome measurement' for all outcomes.
- Assessment of risk of bias in included studies: we added details with regards to assessing risk of bias. We considered all outcomes susceptible to performance bias and assessed them in one group. We redefined subjective and objective outcomes for detection bias.
- Subgroup and sensitivity analysis: we planned to perform subgroup and sensitivity analyses limited to the primary outcomes.
- Appendix: we have summarized the search strategy for each database in [Appendix 1](#).

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-1 Receptor Antagonists [*therapeutic use]; Indoles [*therapeutic use]; Lower Urinary Tract Symptoms [*drug therapy] [etiology]; Naphthalenes [therapeutic use]; Piperazines [therapeutic use]; Prostatic Hyperplasia [*complications]; Quinazolines [therapeutic use]; Randomized Controlled Trials as Topic; Urological Agents [*therapeutic use]

MeSH check words

Aged; Humans; Male