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Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (Review)

Hwang EC, Gandhi S, Jung JH, Imamura M, Kim MH, Pang R, Dahm P

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[Intervention Review]

Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH) is a common condition in ageing men that may cause lower urinary tract symptoms (LUTS). Treatment aims are to relieve symptoms and prevent disease-related complications. Naftopidil is an alpha-blocker (AB) that has a high affinity for the A1d receptor that may have advantages in treating LUTS in this setting. This is an update of a Cochrane Review first published in 2009. Since that time, several large randomised controlled trials (RCTs) have been reported, making this update relevant.

Objectives

To evaluate the effects of naftopidil for the treatment of LUTS associated with BPH.

Search methods

We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, LILAC, 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 to 31 May 2018

Selection criteria

We included all parallel RCTs. We also included cross-over design trials.

Data collection and analysis

Two review authors independently classified 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*. Primary outcomes were urological symptom scores, quality of life (QoL) and treatment withdrawals for any reason; secondary outcomes were treatment withdrawals due to adverse events, acute urinary retention, surgical intervention for BPH, and cardiovascular and sexual adverse events. We considered outcomes measured up to 12 months after randomisation as short term, and later than 12 months as long term. We rated the certainty of the evidence according to the GRADE approach.

Main results

We included 22 RCTs with 2223 randomised participants across four comparisons for short-term follow-up. This abstract focuses on only two of four comparisons for which we found data since two comparators (i.e. propiverine and Eviprostat (phytotherapy)) are rarely used. One study comparing naftopidil to placebo did not report any relevant outcomes and was therefore excluded. There were no trials that compared to combination therapy with naftopidil or any 5-alpha reductase inhibitors (5-ARIs) to combination therapy with other ABs and any 5-ARIs.

All included studies were conducted in Asian countries. Study duration ranged from four to 12 weeks. Mean age was 67.8 years, prostate volume was 35.4 mL, and International Prostate Symptom Score was 18.3. We were unable to perform any of the preplanned subgroup analyses based on age and baseline symptom score.

Naftopidil versus tamsulosin

Based on 12 studies with 965 randomised participants, naftopidil may have resulted in little or no difference in urological symptom score (mean difference (MD) 0.47, 95% confidence interval (CI) -0.09 to 1.04 measured on a scale from 0 to 35 with higher score representing increased symptoms), QoL (MD 0.11, 95% CI -0.09 to 0.30; measured on a scale from 0 to 6 with higher scores representing worse QoL), and treatment withdrawals for any reason (risk ratio (RR) 0.92, 95% CI 0.64 to 1.34; corresponding to 7 fewer per 1000 participants, 95% CI 32 fewer to 31 more). Naftopidil may have resulted in little to no difference in sexual adverse events (RR 0.54, 95% CI 0.24 to 1.22); this would result in 26 fewer sexual adverse events per 1000 participants (95% CI 43 fewer to 13 more). We rated the certainty of evidence as moderate for urological symptom score and low for the other outcomes.

Naftopidil versus silodosin

Based on five studies with 652 randomised participants, naftopidil may have resulted in little or no difference in the urological symptom scores (MD 1.04, 95% CI -0.78 to 2.85), QoL (MD 0.21, 95% CI -0.23 to 0.66), and treatment withdrawals for any reason (RR 0.80, 95% CI 0.52 to 1.23; corresponding to 26 fewer per 1000 participants, 95% CI 62 fewer to 32 more). We rated the certainty of evidence as low for all these outcomes. Naftopidil likely reduced sexual adverse events (RR 0.15, 95% CI 0.06 to 0.42; corresponding to 126 fewer sexual adverse events per 1000 participants, 95% CI 139 fewer to 86 fewer). We rated the certainty of evidence as moderate for sexual adverse events.

Authors' conclusions

Naftopidil appears to have similar effects in the urological symptom scores and QoL compared to tamsulosin and silodosin. Naftopidil has similar sexual adverse events compared to tamsulosin but has fewer compared to silodosin.

PLAIN LANGUAGE SUMMARY

Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Review question

What are the effects of naftopidil in men with bothersome urinary symptoms due to an enlarged prostate?

Background

An enlarged prostate (called benign prostatic hyperplasia) can cause bothersome lower urinary tract symptoms such as having to urinate often during the day or at night, having a weak urine stream, and having the feeling of not emptying the bladder completely. A common reason for these complaints is an enlarged prostate, which is common in older men. Naftopidil is a medication that may help with these symptoms and possibly cause fewer unwanted effects than other medications used for this problem. In this review, we compared naftopidil to other medicines.

Study characteristics

We included 22 studies with 2223 men. The average age was 68.0 years. These men had mostly symptoms rated as moderate or severe.

Key results

Naftopidil may have had similar effects on urinary symptoms and QoL compared to tamsulosin and silodosin. In terms of unwanted effects, naftopidil may have had similar unwanted sexual side effects compared to tamsulosin but have fewer compared to silodosin.

Reliability of the evidence

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

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Naftopidil compared to tamsulosin (alpha-blocker) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia
Setting: likely outpatients
Intervention: naftopidil
Comparator: tamsulosin

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with tamsulosin	Risk difference with naftopidil
Urological symptom scores assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: 4-12 weeks	965 (12 RCTs)	⊕⊕⊕◯ **Moderate**[a]	-	The mean urological symptom scores ranged from 9.2 to 10.7 (from 4 studies) and mean change of urological symptom scores ranged from -9.8 to -3.3 (from 8 studies)	MD 0.47 higher (0.09 lower to 1.04 higher)
Quality of life assessed with: IPSS-Quality of Life Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: 4-12 weeks	878 (11 RCTs)	⊕⊕◯◯ **Low**[a,b]	-	The mean quality of life ranged from 2.7 to 3.1 (from 3 studies) and mean change of quality of life ranged from -2.75 to -0.7 (from 8 studies)	MD 0.11 higher (0.09 lower to 0.30 higher)
Treatment withdrawals for any reason Follow-up: 4-12 weeks	668 (8 RCTs)	⊕⊕◯◯ **Low**[a,c]	**RR 0.92** (0.64 to 1.34)	Study population	
				90 per 1000	7 fewer per 1000 (32 fewer to 31 more)

Cardiovascular adverse events Follow-up: 4-12 weeks	824 (9 RCTs)	⊕⊕◯◯ **Low**[a,c]	**RR 0.97** (0.52 to 1.80)	Study population	
				58 per 1000	2 fewer per 1000 (28 fewer to 47 more)
Sexual adverse events Follow-up: 4-12 weeks	397 (5 RCTs)	⊕⊕◯◯ **Low**[a,c]	**RR 0.54** (0.24 to 1.22)	Study population	
				57 per 1000	26 fewer per 1000 (43 fewer to 13 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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.
[b]Downgraded by one level for inconsistency: moderate-to-substantial heterogeneity.
[c]Downgraded by one level for imprecision: confidence interval crossed assumed threshold of clinically important difference.

BACKGROUND

Description of the condition

Benign prostatic hyperplasia (BPH) is a common condition in elderly men and refers to the non-malignant proliferation of smooth muscle, connective tissue, and glandular epithelium within the prostate, which may result in prostatic urethra obstruction (Roehrborn 2008). The exact aetiology of BPH is currently unknown. Several suggestive risk factors are ageing, familial history, changes in hormonal levels, elevated markers of inflammation, and metabolic syndrome (Russo 2015). Cellular proliferations in the periurethral and transition zones lead to the formation of nodular adenomas, potentially distorting the bladder neck and prostatic urethra. Such occurrence of anatomical changes and prostatic obstruction result in lower urinary tract symptoms (LUTS). There are two categories of LUTS; voiding symptoms (which include hesitancy, weak stream, urinary retention, postmicturition dribble, straining, and incomplete emptying) and storage symptoms (such as frequency, urgency, and nocturia) (McVary 2011). Generally, greater severity of LUTS relates to more detrimental quality of life (QoL) and a greater desire for treatment (Agarwal 2014). Patient self-report using a validated urinary symptom scale, such as International Prostate Symptom Score (IPSS), is used to evaluate symptom severity and QoL; this is an integral part of epidemiological and treatment studies (Barry 1995). Increasing IPSS symptom severity (LUTS severity) is also associated with patient perception of bladder condition, which is regarded as men's overall distress and increased healthcare seeking (Chapple 2017). In this Cochrane Review, we used the term BPH as prostatic enlargement with LUTS through which to define the disease condition and potential need for intervention.

Many of the complications of progressive BPH are rare, even though untreated; however, bladder stones, bladder decompensation, urinary tract infections, haematuria, and azotaemia can occur, requiring medical or surgical intervention. BPH has also been related with other medical conditions, reduced QoL, and increased annual healthcare costs (Kaplan 2015; Kozminski 2015; Martin 2014).

Diagnosis

The diagnosis of BPH is based on followed clinical features; a prostate enlargement, bothersome LUTS, and no other identified causes for the urinary problems. The initial evaluation of BPH includes medical history, symptom score questionnaires (IPSS), physical examination including a digital rectal examination, urinalysis, prostate-specific antigen (PSA) blood test, and frequency volume chart (EAU 2017; 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 QoL domain (AUA Practice Guidelines Committee 2003; Barry 1992). Seven symptom domains use a 6-point scale ranging from 0 (none) to 5 (five or more) (Barry 1992). The QoL 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). Another validated symptom score questionnaire, BPH Impact Index (BII), was developed to assess the effect of LUTS/BPH on 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). Symptom score questionnaires should be delivered to objectively identify and quantify LUTS. These are also sensitive to symptom changes and treatment monitoring (EAU 2017; McVary 2011). A digital rectal examination is an important examination and may help to determine the coexistence of prostate cancer. Urinalysis is useful for differential diagnosis to urinary tract infection. Together with a digital rectal examination, a PSA test increases the detection rate of prostate cancer, but would be performed if life expectancy is greater than 10 years and if a diagnosis of prostate cancer would modify the management approach (EAU 2017; McVary 2011). Measurement of urinary flow rates and residual urine are helpful in diagnostic evaluation and treatment response (EAU 2017; McVary 2011). A decreased urinary flow rate and large residual urine are risk factors of symptom aggravation (Crawford 2006). Other tests include radiological imaging, pressure flow study, and urethrocystoscopy are not recommended as a routine diagnostic procedure except in selective conditions which affect treatment decisions (McVary 2011).

Treatment

The role of treatment for any disease process depends on the magnitude of the clinical effect and the incidence and severity of treatment-related morbidity. In addition, the degree of bother resulting from BPH is the main factor for receiving a treatment. A significant proportion of men with LUTS will not choose medical or surgical intervention because the symptoms are not bothersome. These men are suitable for watchful waiting (Netto 1999) and lifestyle modification (Yap 2009). Men who complain of moderate-to-severe bother with symptoms are likely to benefit from medical (alpha-blockers (ABs), 5-alpha reductase inhibitors (5-ARIs), and combination therapy) or surgical treatment (EAU 2017; McVary 2011). ABs reduce smooth muscle tone in the prostate and bladder neck with/without 5-ARIs, which reduces prostate volume by inducing epithelial atrophy. They are an established treatment in LUTS/BPH and have been widely used as first-line therapy since the late 1990s (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 IPSS by 20% to 50% and increase Q_{max} by 15% to 45% (MacDonald 2005; Wilt 2006). ABs are the most commonly prescribed category of drug for LUTS/BPH, accounting for about 70% of all medications prescribed in 2008 (Cornu 2010). Adverse effects of ABs include postural hypotension, dizziness, headache, asthenia, syncope, peripheral oedema, 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 (Brasure 2016; Dahm 2017; EAU 2017). Also, a phosphodiesterase type 5 inhibitor, tadalafil (5 mg once daily), has been licensed for the treatment of male LUTS, and various plant extracts (e.g., Cucurbita pepo; pumpkin seeds, Hypoxis rooperi; South African star grass, Pygeum africanum; bark of the African plum tree, Secale cereale; rye pollen, Serenoa repens; saw palmetto and Urtica dioica; roots of the stinging nettle) have been proposed for the treatment of male LUTS (EAU 2017; Keehn 2016; Oelke 2012). Surgical treatment was considered in cases of symptoms refractory to medical treatment or traditional absolute indications (e.g. acute urinary retention (AUR), recurrent urinary tract infection, bladder stones or diverticula, haematuria, or renal insufficiency) (EAU 2017; McVary 2011).

Description of the intervention

Naftopidil is selective for the A1d adrenergic receptor with a three- to 17-fold higher affinity than for the A1a and A1b adrenergic receptor subtypes based on in vitro studies and was approved in Japan in 1998 (Takei 1999). Naftopidil should be more effective for storage symptoms measured by IPSS due to its selectivity for the bladder via the A1d receptor subtype. Initial randomised controlled trials (RCTs) found no significant difference in IPSS and QoL (QoL) compared with tamsulosin (Ikemoto 2003; Ju 2002). Along with these studies, several RCTs also reported that naftopidil was as effective as tamsulosin (Momose 2007; Nishino 2006). There were no significant differences in the incidence of adverse events between the naftopidil and tamsulosin groups (Ikemoto 2003; Ju 2002; Momose 2007; Nishino 2006; Singh 2013; Ukimura 2008).

How the intervention might work

The A1a adrenergic receptors are a class of G protein-coupled receptors that consist of three homologous subtypes, including A1a, A1b, and A1d receptors. The A1a receptor subtype predominates in the human prostate, bladder neck, and urethra (Lepor 2016; Michel 2000; Schwinn 2008). A1b receptor subtypes are mainly expressed in the peripheral vasculature and are important in the regulation of blood pressure. The A1d receptor is expressed in the detrusor muscle of the bladder and the sacral region of the spinal cord (Lepor 2016; Michel 2000; Schwinn 2008). Naftopidil, which shows greater selectivity for A1d over the A1a subtype, was reported to be more effective in improving storage symptoms than tamsulosin with greater selectivity for the A1a over the A1d subtype (Nishino 2006; Perumal 2015; Ukimura 2008). In addition, experimental studies have shown that A1d-ARs greatly outnumber A1a-ARs in the bladder and are upregulated in bladder outlet obstruction (Hampel 2002). Therefore, naftopidil may have a therapeutic effect for BPH improving obstruction symptoms and storage symptoms with similar vascular adverse effects, such as dizziness, orthostatic hypotension, which were commonly observed in other ABs.

Why it is important to do this review

Naftopidil is not available in Western countries because of non-Asian randomised clinical trials and lack of placebo-controlled trials. Therefore, the potential advantages or harms of naftopidil (selective A1d-AR blockade) in the treatment of LUTS cannot be assessed until a drug with appropriate subtype selectivity becomes available for clinical evaluation (Andersson 2007). One previous Cochrane Review for naftopidil for the treatment of LUTSs compatible with BPH based on RCTs demonstrated that IPSS and QoL improvement were similar to low-dose tamsulosin (0.2 mg/day) but more improved compared to phytotherapy (Eviprostat) and adverse events due to naftopidil were few and usually mild (Garimella 2009). After publication of the Garimella 2009 review, Cochrane introduced more rigorous methodology, which included assessment of risk of bias and production of 'Summary of findings' tables (the GRADE approach). Furthermore, results of several randomised trials for naftopidil have been reported since the Garimella 2009 review. Therefore, the previous review must be considered outdated. This is an update of the Cochrane Review first published in 2009 (Garimella 2009).

OBJECTIVES

To evaluate the effects of naftopidil, for the treatment of LUTS associated with BPH.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel, RCTs 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 had been previously treated with surgery for BPH. We included studies that their data were available separately for analysis rather than using the whole population.

Types of interventions

We investigated the following comparisons of experimental intervention versus comparator intervention. Concomitant interventions were allowed but had to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- Naftopidil.
- Naftopidil plus any 5-ARIs (if available).

In the past, naftopidil 25 mg/day was initially administered, increasing to 50 mg/day to 75 mg/day over an interval of one to two weeks if needed (Yokoyama 2006). Currently, naftopidil 50 mg/day is the initial clinical recommended dosage (Masumori 2011). One study reported that naftopidil 75 mg/day was also useful for Korean men with BPH to improve total IPSS and OABSS (Kwon 2018). We included trials with doses of naftopidil at 25 mg/day, 50 mg/day, and 75 mg/day.

Comparator interventions

- Placebo.
- Other ABs.
- Other ABs plus any 5-ARIs (if available).
- Anticholinergics.
- Phytotherapy. (e.g. plant extracts)

Comparisons

- Naftopidil versus placebo.
- Naftopidil versus other ABs.
- Naftopidil plus any 5-ARIs (If available) versus other ABs plus any 5-ARIs (if available).
- Naftopidil versus anticholinergics.
- Naftopidil versus phytotherapy.

Types of outcome measures

Primary outcomes

- Urological symptom scores.
- QoL.
- 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

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

We used clinically important differences for the outcomes when available to judge the magnitude of the effect in the context of rating the certainty of the evidence in the "Summary of finding' tables (Jaeschke 1989; Johnston 2013). When the mean difference (MD) or risk ratio (RR) was equal to or larger than the minimal clinically important difference (MCID), we assumed that many participants may have gained a clinically meaningful improvement from treatment.
We considered MCID in the IPSS to be 3 point, BII score to be 0.5 points, and IPSS-Quality of Life to be 0.5 points (Barry 1995; Brasure 2016; Rees 2015). 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 RR increase of at least 25% (Guyatt 2011a). We considered outcomes measured up to

and including 12 months after randomisation 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 presented 'Summary of findings' tables reporting the following outcomes listed according to the perceived priority to men with LUTS/BPH.

- Urological symptom scores.
- QoL.
- 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 8 October 2017. The date of last search of all databases was 31 May 2018. 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 (PubMed).
- Embase (Ovid).
- Scopus.
- LILACS (bvsalud.org/en).
- Web of Science.

We also searched the following trials registers on 8 October 2017 and 31 May 2018.

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

Searching other resources

We searched the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports to identify other potentially eligible trials or ancillary publications. We 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 2015 to 2017 and then updated the search in 2018.

Data collection and analysis

Selection of studies

We used reference management software to identify and remove potential duplicate records (EndNote). Two review authors (ECH, JHJ) independently scanned the abstract, title, or both, of remaining records retrieved to determine which studies should be assessed further. Two review authors (ECH, JHJ) 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 designated the study as 'awaiting classification' and contacted study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in the Characteristics of excluded studies table. We presented 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 (ECH, JHJ) 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).
- Number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions such as frequency (e.g. once daily or twice daily) 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 completion of a 2 × 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 attempted to contact authors of included and excluded 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 maximised 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 (SG, JHJ) independently assessed the risk of bias of each included study. 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 for the following domains (Higgins 2011b).

- 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 (e.g. run-in period, absence of washout period in cross-over trial, baseline imbalance).

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 susceptible to bias (subjective outcomes).

- Urological symptom scores.
- QoL.
- Treatment withdrawals for any reason.
- Treatment withdrawals due to adverse events.
- Cardiovascular adverse events.
- Sexual adverse events.

We defined the following outcomes as not susceptible to bias (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 summarised 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 standardised 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-analyses 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 or more studies contributing in a meta-analysis, we used 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. Therefore, we interpreted results carefully.

Data synthesis

We summarised 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 to perform analyses (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to possibly 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 were based on the following observations.

- Relationship between changes in IPSS and participant global ratings of improvement is influenced by the baseline scores (Barry 1995).
- Tolerability of other ABs (as the main comparator) may differ by participant age (Kozminski 2015; Lepor 2007).

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

Sensitivity analysis

We planned to perform sensitivity analyses limited to the primary outcomes 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 certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results) (Guyatt 2008). For each comparison, two review authors (ECH, JHJ) independently rated the certainty of the 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 the 'Summary of findings' tables, 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).

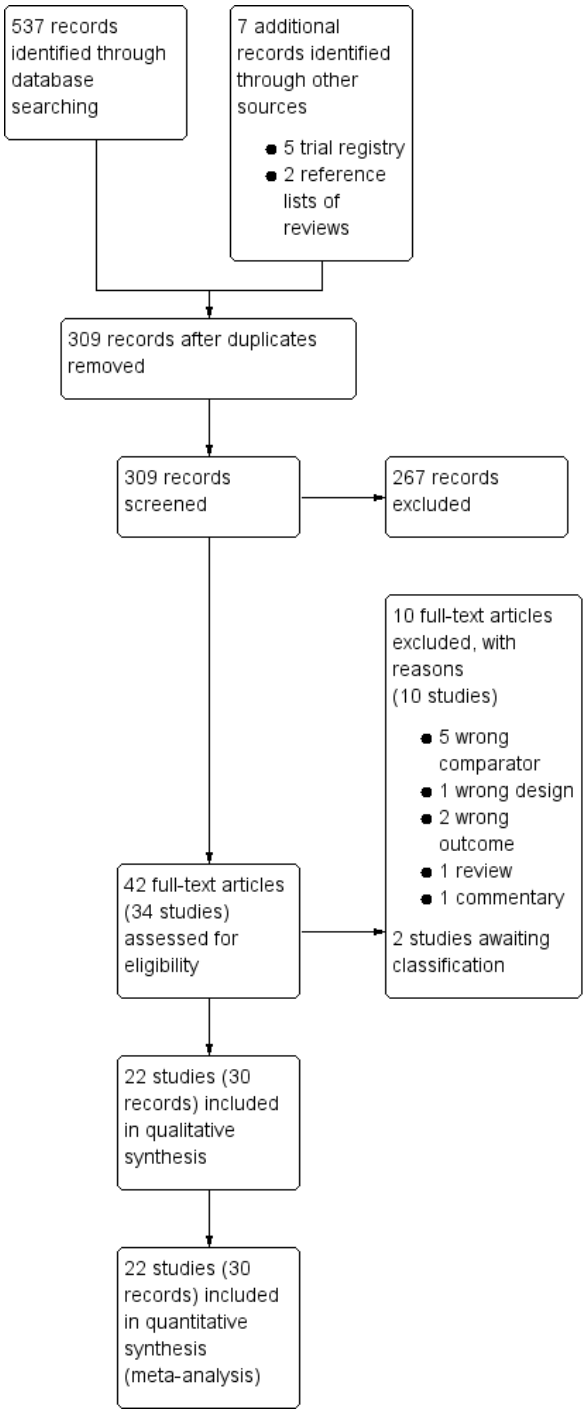
RESULTS

Description of studies

Results of the search

We identified 537 records through electronic database searching, five records in trials registers, and two records in reference lists of reviews. We found no records in the grey literature repository or through handsearching abstract proceedings of relevant meetings from 2015 to 2017. After removal of duplicates, we screened the titles and abstracts of 309 records, and excluded 267 obviously irrelevant records. We screened 42 full-text articles (34 studies), and excluded 10 records (10 studies) that did not meet the inclusion criteria or were not relevant to the review. Two studies are awaiting classification. We included 22 studies (30 records) in the review. The flow of literature through the assessment process is shown in the PRISMA flowchart (Figure 1).

Figure 1. Study flow diagram.



Included studies

Details of included studies are presented in the Characteristics of included studies table; Table 1; and Table 2.

Source of data

We included 21 published studies and one abstract proceeding (Fujihara 2010). Search of the electronic databases identified 21 published studies. Seventeen studies were published in English, three were published in Japanese (Hanyu 2010; Masuda 2012; Ub 2016), and two were published in Chinese (Ju 2002; Li 2007), which were translated into English by two review authors (MI, RP) or 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 three (Kwon 2018; Yamaguchi 2013; Yokoyama 2011; see Appendix 2).

Study design and settings

We included 17 parallel, RCTs (Fujihara 2010; Gotoh 2005; Griwan 2014; Hanyu 2010; Ju 2002; Kwon 2018; Li 2007; Masumori 2009; Matsukawa 2017; Perumal 2015; Shirakawa 2013; Singh 2013; Ukimura 2008; Yamaguchi 2013; Yamanishi 2004; Yokoyama 2009; Yokoyama 2011), and five cross-over trials (Ikemoto 2003; Masuda 2012; Momose 2007; Nishino 2006; Ub 2016). Four of 22 studies were reported as 'double-blinded.' One study blinded participants and investigators (Griwan 2014). Three study were reported to be 'double-blinded' but it was unclear who was blinded (Ju 2002; Nishino 2006; Singh 2013). Three studies were open-label trials (Li 2007; Matsukawa 2017; Shirakawa 2013). The remaining 10 trials had no information regarding blinding. There was one trial with run-in periods (Yamanishi 2004).

All studies were probably conducted in an outpatient clinic setting. Five studies explicitly stated that the trial was conducted in an outpatient clinic setting (Matsukawa 2017; Momose 2007; Perumal 2015; Singh 2013; Yamanishi 2004). All included studies were performed in Asia (Korea, Japan, China, and India). Twelve trials were multicentre (Fujihara 2010; Gotoh 2005; Hanyu 2010; Kwon 2018; Li 2007; Masuda 2012; Masumori 2009; Matsukawa 2017; Ub 2016; Ukimura 2008; Yamaguchi 2013; Yokoyama 2009). The studies were performed from 2002 to 2017.

Participants

We included 2223 randomised participants (naftopidil 1086, tamsulosin 723, silodosin 383, propiverine 18, Eviprostat 13), of which 1612 completed the trials (naftopidil 793, tamsulosin 451, silodosin 337, propiverine 18, Eviprostat 13). However, two studies that compared naftopidil to tamsulosin did not report the number of participants randomised to each group (Ub 2016; Ukimura 2008), and four studies did not report the number of participants who completed the trial in each group (Fujihara 2010; Kwon 2018; Li 2007; Perumal 2015). All studies included men aged over 40 years. The mean age was 67.8 years, prostate volume was 35.4 mL, and IPSS was 18.3.

All studies included participants with LUTS. Three studies included participants with IPSS more than 13 (Griwan 2014; Ju 2002; Li 2007). Four studies did not specify the inclusion criteria for LUTS in detail (Fujihara 2010; Momose 2007; Nishino 2006; Perumal 2015). One study included participants who had been taking tamsulosin for eight weeks; however, participants had persistent overactive bladder symptoms (Kwon 2018). Ten studies used a Q_{max} of 15 mL/s as an inclusion criterion (Gotoh 2005; Griwan 2014; Ikemoto 2003; Ju 2002; Li 2007; Matsukawa 2017; Shirakawa 2013; Singh 2013; Ukimura 2008; Yamanishi 2004). Major exclusion criteria included LUTS from any cause other than BPH, prior treatment with other BPH medical therapy, recent AUR, raised PSA level suspicious of prostate cancer, history of prostate cancer, or prior prostate-related surgery.

Interventions

All studies administered naftopidil as an oral dose of 25 mg to 75 mg once daily.

Comparators

Studies used four different comparators, namely tamsulosin, silodosin, propiverine, and Eviprostat. All comparators were administrated orally. Tamsulosin was administered as an oral dose of 0.2 mg (Fujihara 2010; Gotoh 2005; Hanyu 2010; Ikemoto 2003; Ju 2002; Kwon 2018; Li 2007; Masumori 2009; Momose 2007; Nishino 2006; Ukimura 2008; Yokoyama 2011), or 0.4 mg once daily (Griwan 2014; Perumal 2015; Singh 2013). One study used tamsulosin 0.2 mg plus solifenacin 5 mg once daily as a comparator (Ub 2016). Silodosin was administered as an oral dose of 4 mg to 8 mg once daily (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). Propiverine was administered as an oral dose of 20 mg once daily (Yokoyama 2009). Eviprostat was administered as an oral dose of six tablets once daily (Yamanishi 2004).

Nine studies had a duration of intervention of 12 weeks (Fujihara 2010; Gotoh 2005; Griwan 2014; Hanyu 2010; Masumori 2009; Matsukawa 2017; Singh 2013; Yamaguchi 2013; Yokoyama 2011). Six studies followed the participants for four weeks to eight weeks (Ju 2002; Kwon 2018; Shirakawa 2013; Ukimura 2008;

Yamanishi 2004; Yokoyama 2009). Li 2007 reported 12-month follow-up data. For cross-over trials, two trials reported four weeks' follow-up (Momose 2007; Nishino 2006), one trial reported six weeks' follow-up (Masuda 2012), and two trials reported eight weeks' follow-up (Ikemoto 2003; Ub 2016), before the cross-over.

Comparisons

We included four comparisons in this review: 16 studies compared naftopidil to tamsulosin (Fujihara 2010; Gotoh 2005; Griwan 2014; Hanyu 2010; Ikemoto 2003; Ju 2002; Kwon 2018; Li 2007; Masumori 2009; Momose 2007; Nishino 2006; Perumal 2015; Singh 2013; Ub 2016; Ukimura 2008; Yokoyama 2011), five studies compared naftopidil to silodosin (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011), one study compared naftopidil to propiverine (Yamanishi 2004), and one study compared naftopidil to Eviprostat (Yamanishi 2004). All studies used naftopidil or other ABs as monotherapy. None of the trials compared combination therapy with naftopidil 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. Several studies did not report our predefined secondary outcomes. However, we were able to obtain additional information by contact with the study authors (Kwon 2018; Yamaguchi 2013; Yokoyama 2011). 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

One study reported no funding source (Fujihara 2010), and three reported the funding source (one supported by National program (Li 2007), and two supported by a university (Nishino 2006; Perumal 2015)). The remaining trials did not mention a funding source. Seven studies reported no conflicts of interest (Gotoh 2005; Griwan 2014; Nishino 2006; Perumal 2015; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2009). The remaining studies did not mention conflicts of interest.

Excluded studies

We excluded 10 studies (10 records) out of 34 studies (41 records) after evaluation of the full-text publications. One study was a commentary (Carson 2017) and one was a review (Ikemoto 2010). Five studies had an ineligible comparator (Hiroshi 2011; Maruyama 2006; Sakai 2011; Tsuritani 2010; Yokoyama 2006). One study had an ineligible study design (Hayashi 2002). Two studies had an ineligible study outcome (Yamaguchi 1992; Yamaguchi 1997). However, since there was the possibility that outcomes of interest were measured but not reported, we contacted the first author of the studies and received replies (see Appendix 2). Details of excluded studies are presented in the Characteristics of excluded studies table.

Studies awaiting classification

We found two studies awaiting classification, which did not provide usable outcome data (NCT01203371; NCT01922375; see Characteristics of studies awaiting classification table).

Ongoing trials

We found no ongoing studies.

Risk of bias in included studies

See the 'Risk of bias' table within the Characteristics of included studies table for further details; Figure 2; and Figure 3.

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

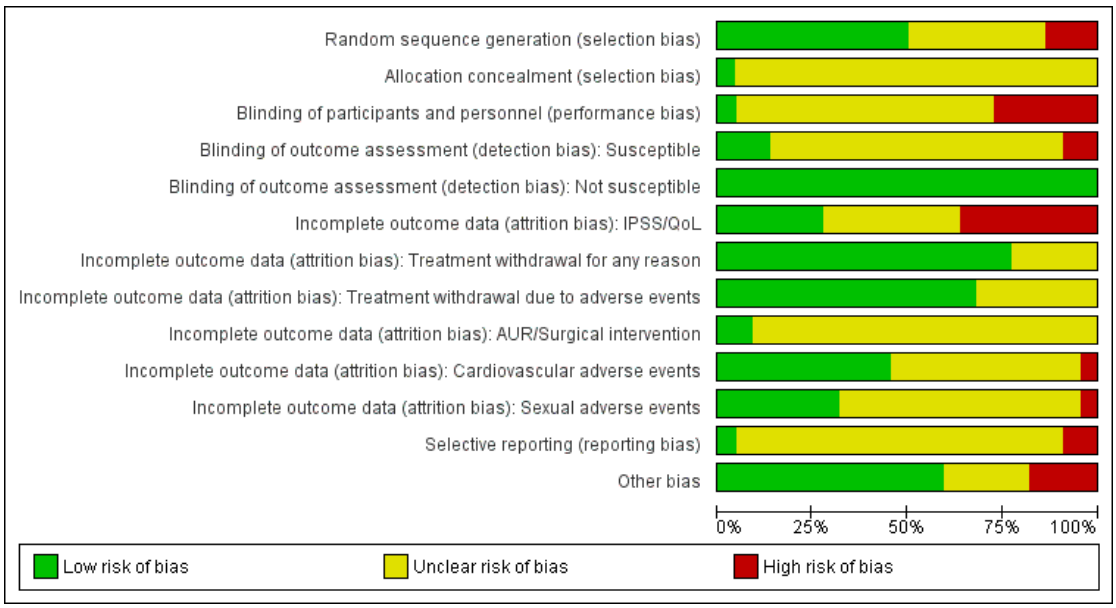
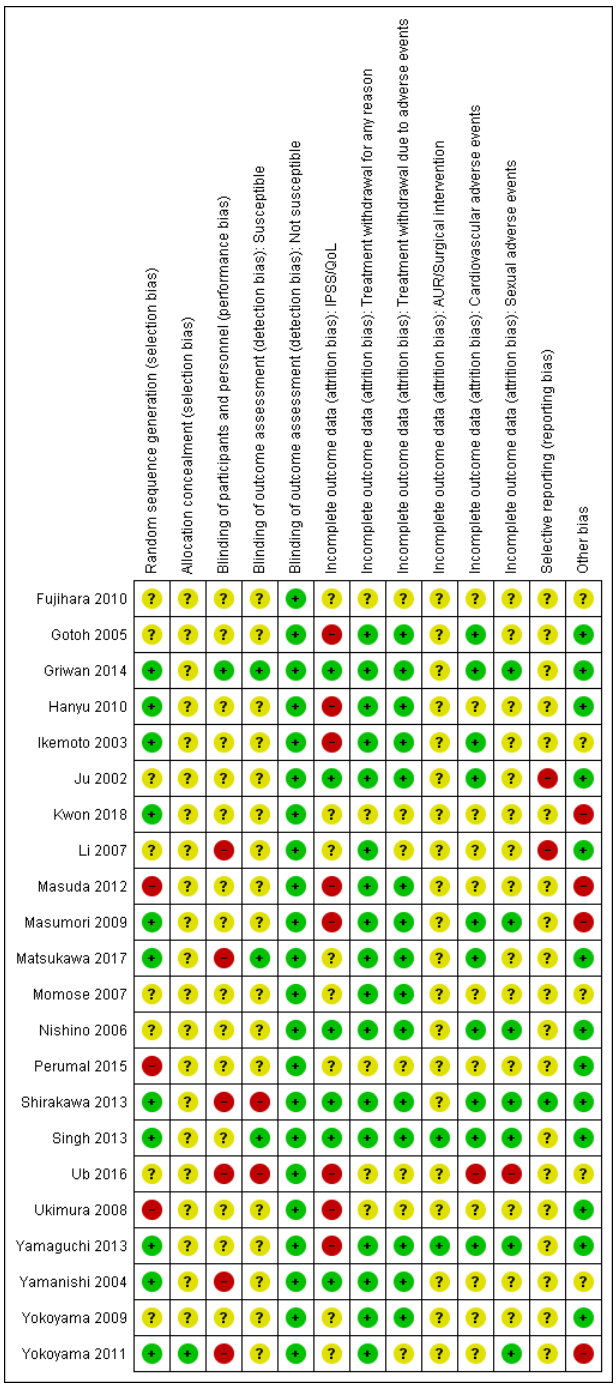


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

- We rated 11 studies at low risk of bias (Griwan 2014; Hanyu 2010; Ikemoto 2003; Kwon 2018; Masumori 2009; Matsukawa 2017; Shirakawa 2013; Singh 2013; Yamaguchi 2013; Yamanishi 2004; Yokoyama 2011), and three studies at high risk of bias (Masuda 2012; Perumal 2015; Ukimura 2008). The remaining studies were at unclear risk of bias.

Allocation concealment

- We rated one study at low risk of bias (Yokoyama 2011); the remaining studies were at unclear risk of bias.

Blinding

Blinding of participants and personnel

- We rated one study at low risk of bias (Griwan 2014). We judged six studies at high risk of bias (Li 2007; Matsukawa 2017; Shirakawa 2013; Ub 2016; Yamanishi 2004; Yokoyama 2011), and the remaining studies at unclear risk of bias.

Blinding of outcome assessment

- Susceptible (subjective: urological symptom scores, QoL, treatment withdrawal for any reason, treatment withdrawal due to adverse events, cardiovascular adverse events, and sexual adverse events) outcomes: we rated three studies at low risk of bias for susceptible (subjective) outcomes (Griwan 2014; Matsukawa 2017; Singh 2013). We judged two studies at high risk of bias (Shirakawa 2013; Ub 2016), and the remaining studies at unclear risk of bias.
- Not susceptible (objective: AUR and surgical intervention for LUTS/BPH) outcomes: we rated all studies at low risk of bias for objective outcomes because objective outcomes are unlikely to be affected by lack of blinding.

Incomplete outcome data

- Urological symptom scores and QoL: we rated six studies at low risk of bias (Griwan 2014; Ju 2002; Nishino 2006; Shirakawa 2013; Singh 2013; Yamanishi 2004). We judged eight studies at high risk of bias (Gotoh 2005; Hanyu 2010; Ikemoto 2003; Masuda 2012; Masumori 2009; Ub 2016; Ukimura 2008; Yamaguchi 2013), and the remaining studies at unclear risk of bias.
- Treatment withdrawal for any reason: we rated 17 studies at low risk of bias (Gotoh 2005; Griwan 2014; Hanyu 2010; Ikemoto 2003; Ju 2002; Li 2007; Masuda 2012; Masumori 2009; Matsukawa 2017; Momose 2007; Nishino 2006; Shirakawa 2013; Singh 2013; Yamaguchi 2013; Yamanishi 2004; Yokoyama 2009; Yokoyama 2011), and the remaining at unclear risk of bias.
- Treatment withdrawal due to adverse events: we rated 15 studies at low risk of bias (Gotoh 2005; Griwan 2014; Hanyu 2010; Ikemoto 2003; Ju 2002; Masuda 2012; Masumori 2009; Matsukawa 2017; Momose 2007; Nishino 2006, Shirakawa 2013; Singh 2013; Yamaguchi 2013; Yamanishi 2004; Yokoyama 2009), and the remaining studies at unclear risk of bias.
- AUR and surgical intervention for LUTS/BPH: we rated two studies at low risk of bias (Singh 2013; Yamaguchi 2013), and the remaining studies at unclear risk of bias.
- Cardiovascular adverse events: we rated 10 studies at low risk of bias (Gotoh 2005; Griwan 2014; Ikemoto 2003; Ju 2002; Masumori 2009; Matsukawa 2017; Nishino 2006; Shirakawa 2013; Singh 2013; Yamaguchi 2013), and one study at high risk of bias (Ub 2016). The remaining studies were at unclear risk of bias.
- Sexual adverse events: we rated seven studies at low risk of bias (Griwan 2014; Masumori 2009; Nishino 2006; Shirakawa 2013; Singh 2013; Yamaguchi 2013; Yokoyama 2011), and one study at high risk bias (Ub 2016). The remaining studies were at unclear risk of bias.

Selective reporting

- We rated one study at low risk of bias (Shirakawa 2013). We judged two studies) at high risk of bias (Ju 2002; Li 2007), and the remaining studies at unclear risk of bias.

Other potential sources of bias

- We rated 13 studies at low risk of bias (Gotoh 2005; Griwan 2014; Hanyu 2010; Ju 2002; Li 2007; Matsukawa 2017; Nishino 2006; Perumal 2015; Shirakawa 2013; Singh 2013; Ukimura 2008; Yamaguchi 2013; Yokoyama 2009). We judged four studies at high risk of bias due to clinically important imbalances in baseline characteristics and for selectively enrolling participants who had a poor response to other ABs (Kwon 2018; Masuda 2012; Masumori 2009; Yokoyama 2011). The remaining studies were at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Naftopidil compared to tamsulosin (alpha-blocker) for the treatment of

lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term); **Summary of findings 2** Naftopidil compared to silodosin (alpha-blocker) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term); **Summary of findings 3** Naftopidil compared to propiverine (anticholinergic) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term); **Summary of findings 4** Naftopidil compared to Eviprostat (phytotherapy) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term)

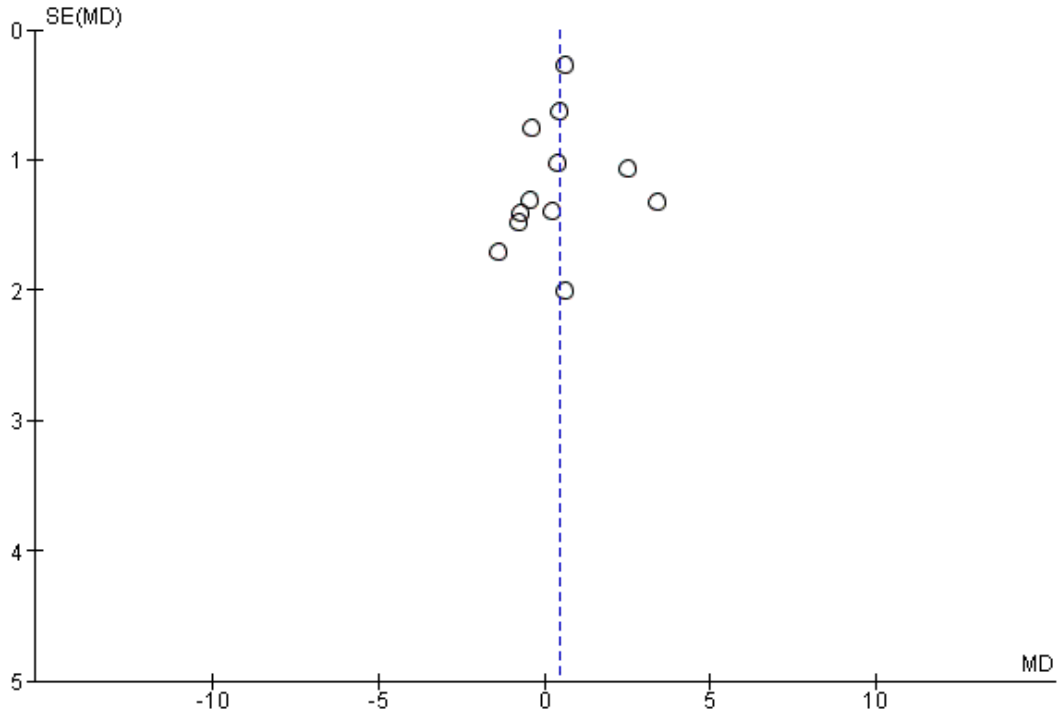
1. Naftopidil versus tamsulosin

See: Summary of findings for the main comparison.

1.1. Urological symptom scores

We included 12 RCTs with 965 participants in the analysis (naftopidil 482, tamsulosin 483) (Fujihara 2010; Gotoh 2005; Griwan 2014; Hanyu 2010; Ikemoto 2003; Ju 2002; Kwon 2018; Masumori 2009; Momose 2007; Nishino 2006; Ukimura 2008; Yokoyama 2011). We used the final value in four studies (Ikemoto 2003; Nishino 2006; Ukimura 2008; Yokoyama 2011), and change from baseline in the remaining studies. Naftopidil may have resulted in little to no difference in urological symptom scores (MD 0.47, 95% CI -0.09 to 1.04; I^2 = 17%). We rated the certainty of the evidence as moderate, downgrading for study limitations (Analysis 1.1). The funnel plot showed symmetry thereby suggesting no publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 Naftopidil versus tamsulosin, outcome: 1.1 International Prostate Symptom Score.

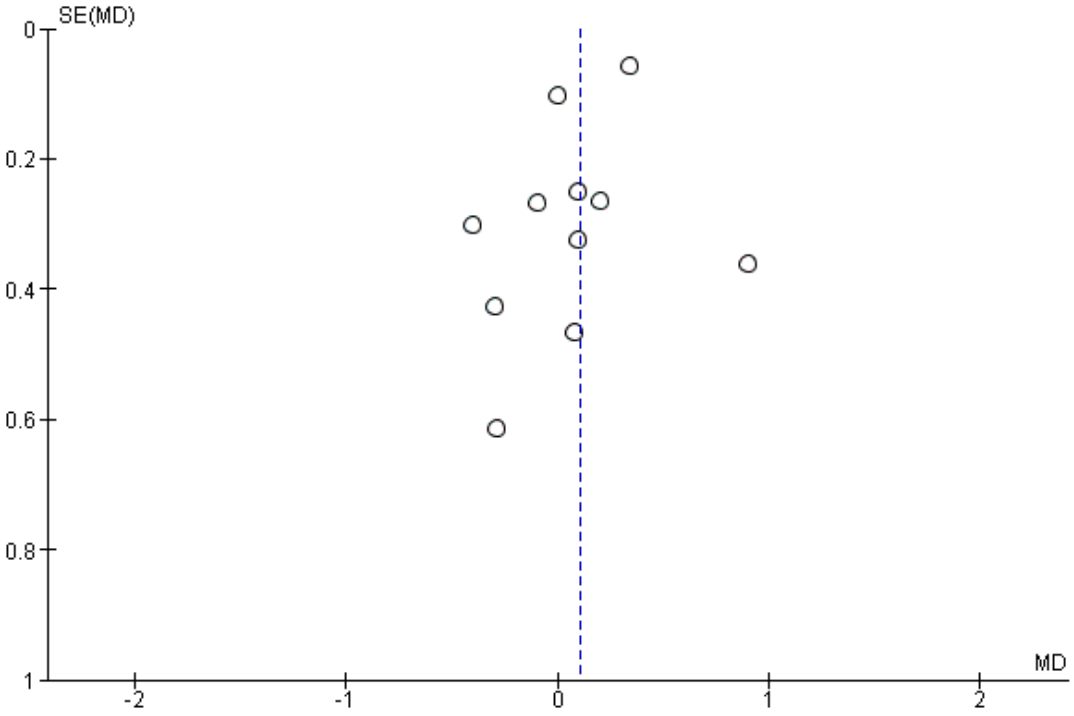


1.2. Quality of life

We included 11 RCTs with 878 participants in the analysis (naftopidil 434, tamsulosin 444) (Fujihara 2010; Gotoh 2005; Griwan 2014; Hanyu 2010; Ikemoto 2003; Kwon 2018; Masumori 2009; Momose 2007; Nishino 2006; Ukimura 2008; Yokoyama 2011).

We used final value in three studies (Ikemoto 2003; Nishino 2006; Ukimura 2008), and change from baseline in the remaining studies. Naftopidil may have resulted in little to no difference in QoL (MD 0.11, 95% CI -0.09 to 0.30; I^2 = 52%). We rated the certainty of the evidence as low, downgrading for study limitations, inconsistency, and concerns about publication bias due to funnel plot asymmetry (Analysis 1.2; Figure 5).

Figure 5. Funnel plot of comparison: 1 Naftopidil versus tamsulosin, outcome: 1.2 International Prostate Symptom Score-Quality of Life.



1.3. Treatment withdrawal for any reason

We included eight RCTs with 668 participants in the analysis (naftopidil 335, tamsulosin 333) (Griwan 2014; Hanyu 2010; Ju 2002; Masumori 2009; Momose 2007; Nishino 2006; Singh 2013; Yokoyama 2011). Naftopidil may have resulted in little to no difference in treatment withdrawal for any reason (RR 0.92, 95% CI 0.64 to 1.34; I^2 = 0%). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 1.3).

1.4. Treatment withdrawals due to adverse events

We included nine RCTs with 735 participants in the analysis (naftopidil 366, tamsulosin 369) (Griwan 2014; Hanyu 2010; Ikemoto 2003; Ju 2002; Masumori 2009; Momose 2007; Nishino 2006; Singh 2013; Yokoyama 2011). For the cross-over trials, we used only the number of participants who had been initially randomised due to lack of information about the number of participants in the analysis (Ikemoto 2003; Momose 2007). Naftopidil may have resulted in little to no difference in treatment withdrawal due to adverse events (RR 1.82, 95% CI 0.72 to 4.61; I^2 = 0%). We rated the certainty of the evidence as low downgrading for

study limitations and imprecision (Analysis 1.4).

1.5. Acute urinary retention

We included three RCTs with 272 participants in the analysis (naftopidil 142, tamsulosin 130) (Hanyu 2010; Singh 2013; Yokoyama 2011). We found no events for AUR in two studies (Hanyu 2010; Yokoyama 2011). Naftopidil likely resulted in little to no difference in AUR (RR 0.82, 95% CI 0.23 to 2.86). We rated the certainty of the evidence as moderate, downgrading for imprecision (few events, few participants, and wide CIs) (Analysis 1.5).

1.6. Surgical intervention for lower urinary tract symptoms/benign prostatic hyperplasia

We included two RCTs with 171 participants in the analysis (naftopidil 92, tamsulosin 79) (Hanyu 2010; Yokoyama 2011). There were no events for surgical intervention for LUTS/BPH in either group (Analysis 1.6).

1.7. Cardiovascular adverse events

We included nine RCTs with 824 participants in the analysis (naftopidil 413, tamsulosin 411) (Gotoh 2005; Griwan 2014; Hanyu 2010; Ju 2002; Masumori 2009; Momose 2007; Nishino 2006; Singh 2013; Yokoyama 2011). For cross-over trials, we took all measurements from naftopidil periods and all measurements from tamsulosin periods (Momose 2007). Naftopidil may have resulted in little to no difference in cardiovascular adverse events (RR 0.97, 95% CI 0.52 to 1.80; I^2 = 14%). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 1.7).

1.8. Sexual adverse events

We included five RCTs with 397 participants in the analysis (naftopidil 204, tamsulosin 193) (Hanyu 2010; Masumori 2009; Nishino 2006; Singh 2013; Yokoyama 2011). Naftopidil may have resulted in little to no difference in sexual adverse events (RR 0.54, 95% CI 0.24 to 1.22; I^2 = 0%). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 1.8).

Subgroup analysis

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

Sensitivity analysis

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

2. Naftopidil versus silodosin

See: Summary of findings 2.

2.1. Urological symptom scores

We included five RCTs with 652 participants in the analysis (naftopidil 327, silodosin 325) (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). We used change from baseline. Naftopidil may have resulted in little to no difference in urological symptom scores (MD 1.04, 95% CI -0.78 to 2.85; I^2 = 84%). We rated the certainty of the evidence as low, downgrading for study limitations and inconsistency (Analysis 2.1).

2.2. Quality of life

We included five RCTs with 652 participants in the analysis (naftopidil 327, silodosin 325) (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). We used change from baseline. Naftopidil may have resulted in little to no difference in QoL (MD 0.21, 95% CI -0.23 to 0.66; I^2 = 92%). We rated the certainty of the evidence as low, downgrading for study limitations and inconsistency (Analysis 2.2).

2.3. Treatment withdrawals for any reason

We included four RCTs with 659 participants in the analysis (naftopidil 325, silodosin 334) (Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). Naftopidil may have resulted in little to no difference in treatment withdrawal for any reason (RR 0.80, 95% CI 0.52 to 1.23; I^2 = 0%). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 2.3).

2.4. Treatment withdrawals due to adverse events

We included five RCTs with 738 participants in the analysis (naftopidil 366, silodosin 372) (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). For the cross-over trial, we used only the number of participants who had been initially randomised due to lack of information about the number of participants in the analysis (Masuda 2012). Naftopidil may have resulted in little to no difference in treatment withdrawal due to adverse events (RR 0.72, 95% CI 0.35 to 1.51; I^2 = 0%). We rated the certainty of the evidence as low downgrading for study limitations and imprecision (Analysis 2.4).

2.5. Acute urinary retention

We included two RCTs with 180 participants in the analysis (naftopidil 86, silodosin 94) (Yamaguchi 2013; Yokoyama 2011). There were no events for AUR in either group (Analysis 2.5).

2.6. Surgical intervention for lower urinary tract symptoms/benign prostatic hyperplasia

We included two RCTs with 180 participants in the analysis (naftopidil 86, silodosin 94) (Yamaguchi 2013; Yokoyama 2011). There were no events for surgical intervention for LUTS/BPH in either group (Analysis 2.6).

2.7. Cardiovascular adverse events

We included five RCTs with 808 participants in the analysis (naftopidil 397, silodosin 411) (Masuda 2012; Matsukawa 2017; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). For the cross-over trial, we took all measurements from naftopidil periods and all measurements from silodosin periods (Masuda 2012). Naftopidil may have resulted in little to no difference in cardiovascular adverse events (RR 0.98, 95% CI 0.39 to 2.44; I^2 = 0%). We rated the certainty of the evidence as low downgrading for study limitations and imprecision (Analysis 2.7).

2.8. Sexual adverse events

We included four RCTs with 348 participants in the analysis (naftopidil 172, silodosin 176) (Masuda 2012; Shirakawa 2013; Yamaguchi 2013; Yokoyama 2011). For the cross-over trial, we took all measurements from naftopidil periods and all measurements from silodosin periods (Masuda 2012). Naftopidil likely decreased sexual adverse events (RR 0.15, 95% CI 0.06 to 0.42; I^2 = 0%). Naftopidil would result in 126 fewer sexual adverse events per 1000 men (95% CI 139 fewer to 86 fewer). We rated the certainty of the evidence as moderate, downgrading for study limitations (Analysis 2.8).

Subgroup analysis

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

Sensitivity analysis

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

3. Naftopidil versus propiverine

See: Summary of findings 3.

3.1. Urological symptom scores

We included one RCT with 37 participants in the analysis (naftopidil 19, propiverine 18) (Yokoyama 2009). Naftopidil may have resulted in little to no difference in urological symptom scores (MD -2.80, 95% CI -6.99 to 1.39). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 3.1).

3.2. Quality of life

We included one RCT with 37 participants in the analysis (naftopidil 19, propiverine 18) (Yokoyama 2009). Naftopidil may have resulted in little to no difference in QoL (MD 0.10, 95% CI -0.56 to 0.76). We rated the certainty of the evidence as low, downgrading for study limitations and imprecision (Analysis 3.2).

3.3. Treatment withdrawals for any reason; treatment withdrawals due to adverse events; acute urinary retention; surgical intervention for lower urinary tract symptoms/benign prostatic hyperplasia; cardiovascular adverse events; sexual adverse events

We found no studies that reported these outcomes.

Subgroup analysis

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

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

4. Naftopidil versus Eviprostat

See: Summary of findings 4.

4.1. Urological symptom scores

We included one RCT with 49 participants in the analysis (naftopidil 36, Eviprostat 13) (Yamanishi 2004). Naftopidil likely reduced urological symptom scores (MD -6.30, 95% CI -9.46 to -3.14). We rated the certainty of the evidence as moderate, downgrading for study limitations (Analysis 4.1).

4.2. Quality of life

We included one RCT with 49 participants in the analysis (naftopidil 36, Eviprostat 13) (Yamanishi 2004). Naftopidil likely increased QoL (MD -1.50, 95% CI -2.36 to -0.64). We rated the certainty of the evidence as moderate, downgrading for study limitations (Analysis 4.2).

4.3. Treatment withdrawals for any reason

We included one RCT with 49 participants in the analysis (naftopidil 36, Eviprostat 13) (Yamanishi 2004). There were no events for treatment withdrawal for any reason (Analysis 4.3).

4.4. Treatment withdrawals due to adverse events

We included one RCT with 49 participants in the analysis (naftopidil 36, Eviprostat 13) (Yamanishi 2004). There were no events for treatment withdrawal due to adverse events (Analysis 4.4).

4.5. Acute urinary retention; surgical intervention for lower urinary tract symptoms/benign prostatic hyperplasia; cardiovascular adverse events; sexual adverse events

We found no studies that reported these outcomes.

Subgroup analysis

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

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Naftopidil compared to silodosin (alpha-blocker) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia
Setting: likely outpatients
Intervention: naftopidil
Comparator: silodosin

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with silodosin	Risk difference with naftopidil
Urological symptom scores Assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: 6-12 weeks	652 (5 RCTs)	⊕⊕◯◯ **Low**[a,b]	-	The mean change of urological symptom scores ranged from -8.6 to -4.9	MD 1.04 higher (0.78 lower to 2.85 higher)
Quality of life Assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: 6-12 weeks	652 (5 RCTs)	⊕⊕◯◯ **Low**[a,b]	-	The mean change of quality of life ranged from -2.0 to -0.98	MD 0.21 higher (0.23 lower to 0.66 higher)
Treatment withdrawals for any reason Follow-up: 8-12 weeks	659 (4 RCTs)	⊕⊕◯◯ **Low**[a,c]	**RR 0.80** (0.52 to 1.23)	Study population	
				129 per 1000	26 fewer per 1000 (62 fewer to 30 more)
Cardiovascular adverse events Follow-up: 6-12 weeks	808 (5 RCTs)	⊕⊕◯◯ **Low**[a,c]	**RR 0.98** (0.39 to 2.44)	Study population	

				24 per 1000	0 fewer per 1000 (15 fewer to 35 more)
Sexual adverse events Follow-up: 6-12 weeks	348 (4 RCTs)	⊕⊕⊕◯ **Moderate**[a]	**RR 0.15** (0.06 to 0.42)	Study population	
				148 per 1000	126 fewer per 1000 (139 fewer to 86 fewer)

*__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; **IPSS-QoL:** International Prostate Symptom Score - Quality of Life; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.
[b]Downgraded by one level for inconsistency: substantial heterogeneity.
[c]Downgraded by one level in imprecision: confidence interval crossed assumed threshold of clinically important difference.

Naftopidil compared to propiverine (anticholinergic) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia
Setting: likely outpatients
Intervention: naftopidil
Comparator: propiverine

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with propiverine	Risk difference with naftopidil
Urological symptom scores assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 4 weeks	37 (1 RCT)	⊕⊕◯◯ **Low**[a,b]	-	The mean change of urological symptom scores was -2.1	MD 2.8 lower (6.99 lower to 1.39 higher)
Quality of life assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: mean 4 weeks	37 (1 RCT)	⊕⊕◯◯ **Low**[a,b]	-	The mean change of quality of life was -1.0	MD 0.1 higher (0.56 lower to 0.76 higher)
Treatment withdrawals for any reason[c] follow-up: mean 4 weeks	37 (1 RCT)	-	Not reported	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Cardiovascular adverse events[c] follow-up: mean 4 weeks	37 (1 RCT)	-	Not reported	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

Sexual adverse events[c] follow-up: mean 4 weeks	37 (1 RCT)	-	Not reported	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

*__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; **IPSS-QoL:** International Prostate Symptom Score - Quality of Life; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level for study limitations: unclear risk of selection, performance, detection, and reporting bias.
[b]Downgraded by one level for imprecision: confidence interval crossed assumed threshold of clinically important difference of IPSS 3 and quality of life 0.5.
[c]Treatment withdrawal due to any reasons; cardiovascular adverse events; and sexual adverse events: no available data.

Naftopidil compared to Eviprostat (phytotherapy) for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (short term)

Participants: men with lower urinary tract symptoms suggesting benign prostatic hyperplasia
Setting: likely outpatients
Intervention: naftopidil
Comparator: Eviprostat

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Eviprostat	Risk difference with Naftopidil
Urological symptom scores assessed with: IPSS Scale from: 0 (best: not at all) to 35 (worst: almost always) Follow-up: mean 6 weeks	49 (1 RCT)	⊕⊕⊕◯ **Moderate**[a]	-	The mean change of urological symptom scores was 0.4	MD 6.3 lower (9.46 lower to 3.14 lower)
Quality of life assessed with: IPSS-QoL Scale from: 0 (best: delighted) to 6 (worst: terrible) Follow-up: mean 6 weeks	49 (1 RCT)	⊕⊕⊕◯ **Moderate**[a]	-	The mean change of quality of life was 0	MD 1.5 lower (2.36 lower to 0.64 lower)
Treatment withdrawals for any reason Follow-up: mean 6 weeks	49 (1 RCT)	⊕⊕◯◯ **Very low**[a,b]	RR approximately 1 with wide CI	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Treatment withdrawals due to adverse events Follow-up: mean 6 weeks	49 (1 RCT)	⊕⊕◯◯ **Very low**[a,b]	RR approximately 1 with wide CI	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

Cardiovascular adverse events[c] Follow-up: mean 6 weeks	49 (1 RCT)	-	Not reported	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Sexual adverse events[c] Follow-up: mean 6 weeks	49 (1 RCT)	-	Not reported	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

***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; **IPSS-QoL:** International Prostate Symptom Score - Quality of Life; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.
[b]Downgraded by two level for imprecision: RR approximately 1 with wide confidence interval and no events.
[c]Cardiovascular adverse events and sexual adverse events: no available data.

DISCUSSION

Summary of main results

We included 22 unique studies with 2223 randomised participants across four comparisons for short-term follow-up (up to 12 weeks). We found no longer-term data.

We were unable to compare naftopidil to placebo. The only available study did not report on any outcome relevant to this review (Yamaguchi 1997).

Compared to tamsulosin, naftopidil may have had a similar effect on urological symptom scores, QoL, and treatment withdrawals for any reason (primary outcomes). It may have had a similar effect on treatment withdrawals due to adverse event, AUR, surgical intervention for LUTS/BPH, cardiovascular adverse events, and sexual adverse events (secondary outcomes).

Findings were similar when comparing naftopidil to silodosin with the exception of sexual adverse events, which were substantially reduced by naftopidil. Naftopidil resulted in 123 fewer sexual adverse events per 1000 men (95% CI 139 fewer to 80 fewer) compared to silodosin.

The body of evidence comparing naftopidil to other ABs was limited. Compared to propiverine, naftopidil may have had similar effects on urological symptom scores and QoL. We found no studies that reported other outcomes. Compared to Eviprostat, naftopidil likely resulted in a clinically important reduction in urological symptom scores and improved QoL. There were no treatment withdrawals for any reason or due to adverse events.

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

Overall completeness and applicability of evidence

In this review update, we used up-to-date Cochrane methods and added 16 news trials. Despite a large body of evidence informing this review, the following issues deserve consideration.

- In contrast to the previous version of this review, we identified one trial comparing naftopidil to placebo (Yamaguchi 1997). We could not use the study results because the study did not report on any outcomes relevant to this review. This information was confirmed by direct communication with the study investigators.
- Our ability to assess the longer-term outcomes of naftopidil compared to other drugs was limited given that all trials had a short duration of follow-up of 12 weeks or less. Therefore, we were unable to assess the longer-term efficacy and adverse effects of naftopidil.
- Aside from three studies that used tamsulosin 0.4 mg (Griwan 2014; Perumal 2015; Singh 2013), most studies comparing naftopidil to tamsulosin 0.2 mg, which is lower than the recommended dose in Western countries and is based on a lower mean body size in Asian countries. Therefore, general applicability of this body of evidence to non-Asian men is uncertain.
- We were unable to determine the effect of naftopidil on AUR or surgical interventions due to the lack of events in the included studies. This related to the short follow-up period. Additional information may have to be drawn from longer-term observational studies.
- Although ABs such as naftopidil are commonly used in combination with 5-ARIs, we found no eligible studies.

Quality of the evidence

We consistently downgraded the certainty of the evidence by one or two levels to moderate or low. The most common reasons for downgrading were study limitations (issues surrounding allocation concealment, blinding, and incomplete outcome data), clinically important inconsistency (with high I^2 values, which we were unable to explain through secondary analyses), and imprecision (wide CIs that crossed the assumed threshold of clinically important difference or few events, or both). We also detected some cases of potential publication bias due to the observed funnel plot asymmetry.

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 including other Asian countries (India, China, Korea). However, this regional problem might not be resolved in future study because naftopidil was only approved these countries to treat men with BPH. 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. All Japanese and Chinese literature were translated into English by two review authors (MI, RP) with appropriate language skills. We used Google translator to double check the translated data. However, the lack of human double-data abstraction may be considered a potential source of bias. We investigated reporting bias using funnel plots, which showed no symmetry for IPSS (Figure 4) and asymmetry for QoL in naftopidil and tamsulosin comparison arms (Figure 5). We attempted to contact all the study authors on several occasions seeking feedback. While we received additional information from three study authors, others did not reply. This may represent a source of bias. For cross-over trials, we tried to extract the data from first period (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 used the event rate to report individual adverse events, which may result in a unit of analysis error (double counting) (Masuda

2012; Singh 2013). For other cross-over trials, we used the number of participants initially randomised as a more conservative approach.

Agreements and disagreements with other studies or reviews

Two systematic reviews and meta-analyses reported that naftopidil had a similar effect on urological symptom scores and bladder outlet obstruction indices compared to other ABs (Fusco 2016; Yuan 2015). Along with a previous Cochrane systematic review results (Garimella 2009), one systematic review reported that naftopidil had comparable efficacy to tamsulosin and silodosin (Castiglione 2014). Overall adverse events were reported as 2% to 15%, which was comparable to tamsulosin (Castiglione 2014). The incidence of sexual adverse events was less than compared to silodosin (Castiglione 2014). However, both reviews only included RCTs from Japan and those published in English language. In addition, no meta-analysis was reported and the authors did not rate the certainty of the evidence (Castiglione 2014; Garimella 2009). This updated Cochrane Review used rigorous methodology, exhaustive literature search, and assessment of the certainty of the evidence using GRADE, thereby providing the most reliable evidence summary.

AUTHORS' CONCLUSIONS

Implications for practice

Based on moderate-to-low certainty evidence, the effect of naftopidil appears similar to tamsulosin with regards to urological symptom scores, quality of life, and sexual adverse events.

Based on low-certainty evidence, the effect of naftopidil appears similar to silodosin for urological symptom scores and quality of life. However, it probably has fewer sexual adverse events compared to silodosin based on moderate-certainty evidence. This information is important for the counselling of sexually active men.

Implications for research

Our knowledge could be improved by focus on the following issues.

- Given that patients take alpha-blockers for extended periods of time (typically years), there is a critical need for long-term studies of safety and efficacy of naftopidil. Such studies would also help to inform the outcome of acute urinary retention and surgical interventions for benign prostatic hyperplasia.

- Several trials included in this review used suboptimal dose of naftopidil (25 mg) and silodosin (4 mg). This may result in an underestimate of both the beneficial effects and the potential adverse events. Unfortunately, we were unable explore this and other questions around possible subgroup effects (based on patient age and baseline International Prostate Symptom Score) in subgroup analyses.

- Most included studies had considerable methodological limitations. It would be preferable if future studies applied appropriate allocation concealment, blinding of all relevant parties (participants, personnel, and outcome assessors), strove for complete or near-complete follow-up, and had reporting transparency.

- 5-alpha reductase inhibitors (e.g. finasteride and dutasteride) and phosphodiesterase inhibitors (e.g. tadalafil) have been used to treat lower urinary tract infections. Future studies are needed to compare efficacy and adverse events between these drugs and naftopidil.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Fujihara 2010

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre/Japan **Study dates:** NR
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS with OAB symptoms **Exclusion criteria** • NR **Total number of participants randomised** • Screened: NR • Eligible: 82 **Group A** (naftopidil) • Number of participants randomised: 39 • Age: NR • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 17.61 ± 5.8 (estimated from the figure) • Q_{max}: NR **Group B** (tamsulosin) • Number of participants randomised: 43 • Age: NR • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 15.72 ± 6.96 (estimated from the figure) • Q_{max}: NR
Interventions	**Run-in period:** none **Group A:** naftopidil 50-75 mg once daily **Group B:** tamsulosin 0.2 mg once daily **Duration:** 12 weeks
Outcomes	**Primary outcomes** • Change from baseline in total score (questions 1-7) of IPSS, IPSS-QoL, VAS • How measured: questionnaire • Time of measurement: NR • Time at reporting: baseline, 12 weeks **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none
Funding sources	None

Fujihara 2010 (*Continued*)

Declarations of interest	NR
Notes	**Language of publication:** English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "we performed a multi-center randomised controlled study." Comment: randomisation stated but no information on method used was available; therefore, selection bias was at unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear; abstract only
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear; abstract only
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear; abstract only
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only

Fujihara 2010 (*Continued*)

Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear; abstract only
Selective reporting (reporting bias)	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of reporting bias was unclear; abstract only
Other bias	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of other sources of bias was unclear; abstract only

Gotoh 2005

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre (16 investigational sites)/Japan **Study dates:** NR
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men aged ≥ 50 years • IPSS ≥ 8 • Q_{max} < 15 mL/s (voided volume ≥ 150 mL); prostate ≥ 20 mL **Exclusion criteria** • History of allergy to AB • Treatment with antiandrogen drugs • Current therapy with any AB • Drugs with anticholinergic activity • Significant history of orthostatic hypotension • Concomitant neurological diseases • Known or suspected neurogenic bladder dysfunction • Carcinoma of the prostate or bladder • Previous surgery for BPH or bladder neck obstruction • History of recurrent UTI, or concomitant active UTI. **Total number of participants randomised** • Screened: 185 • Eligible: 144 **Group A** (naftopidil) • Number of participants randomised: 69 • Age (years) (mean ± SD): 68.0 ± 7.2 (calculated from 95% CI 66.4 to 69.8) • Prostate volume (mL) (mean ± SD): 29.0 ± 10.2 (calculated from 95% CI 27.2 to 32.0) • PSA: NR

	• IPSS (mean ± SD): 15.5 ± 5.7 (calculated from 95% CI 14.1 to 16.8) • Q_{max} (mL/s) (mean ± SD): 9.3 ± 3.6 (calculated from 95% CI 8.4 to 10.1) **Group B** (tamsulosin) • Number of participants randomised: 75 • Age (years) (mean ± SD): 68.5 ± 6.8 (calculated from 95% CI 67.0 to 70.1) • Prostate volume (mL) (mean ± SD): 33.6 ± 18.1 (calculated from 95% CI 29.5 to 37.7) • PSA: NR • IPSS (mean ± SD): 17.1 ± 6.18 (calculated from 95% CI 15.7 to 18.5) • Q_{max} (mL/s) (mean ± SD): 8.8 ± 3.3 (calculated from 95% CI 8.1 to 9.6)
Interventions	**Run-in period:** none **Group A:** naftopidil 25 mg/day for 2 weeks, followed by 50 mg/day for 10 weeks **Group B:** tamsulosin 0.2 mg/day for 12 weeks **Duration:** 12 weeks
Outcomes	**Primary outcomes** • Change from baseline in the total score (questions 1-7) of IPSS, Q_{max}, PVR • How measured: IPSS questionnaire, uroflowmetry, transabdominal US • Time of measurement: baseline; 2, 4, 8, 12 weeks • Time of reporting: baseline, 12 weeks **Secondary outcomes** • Change from baseline in mean flow rate, IPSS voiding score, IPSS storage score, IPSS-QoL • How measured: IPSS questionnaire, uroflowmetry • Time of measurement: baseline; 2, 4, 8, 12 weeks • Time of reporting: baseline, 12 weeks **Safety outcomes** • Adverse effect • BP changes • How measured; NR, systolic/diastolic BP • Time of measurement: baseline, 12 weeks • Time of reporting: baseline, 12 weeks **Subgroup:** none
Funding sources	NR
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: "prospective, randomised controlled trial" Comment: randomisation stated but no information on method used was available;

Gotoh 2005 (*Continued*)

		therefore, selection bias was at unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 21/90 (23.3%) participants in naftopidil group and 20/95 (21.0%) participants in tamsulosin group not included in analysis; owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes are well described but protocol was not published
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias found; therefore, risk of other bias was low

Griwan 2014

Methods	**Study design:** parallel randomised clinical study **Setting/country:** single institute/India **Study dates:** NR
Participants	**Ethnicity:** Indian **Inclusion criteria** • Aged ≥ 45 years • Daytime frequency > 8, nocturnal frequency > 2 • Q_{max} 5-15 mL/s (150 mL voided volume), PVR < 150 mL • IPSS > 13, IPSS bother score > 3 **Exclusion criteria** • Previous prostate surgery • Severe visceral disease • Postural hypotension • Neurogenic bladder dysfunction, suspected prostate cancer, urethral stricture disease, history of pelvic irradiation, bladder neck disease, acute bacterial prostatitis, acute UTI, urolithiasis, history of concomitant medication that could alter the voiding pattern before inclusion (calcium antagonist, monoamine oxidase inhibitors, or anticholinergic drugs) • Active haematuria • Renal insufficiency (serum creatinine > 2.0 mg/dL), severe hepatic impairment (transaminases > 2 times the upper normal limit or total bilirubin > 1.5 mg/dL, or both) • People taking antipsychotic medications, insulin-dependent diabetes mellitus, history of severe heart disease (myocardial infarction or cerebrovascular accident in the previous 6 months), ascertained or suspected hypersensitivity to tamsulosin and naftopidil **Total number of participants randomised** • Screened: NR • Eligible: 120 **Group A** (naftopidil) • Number of participants randomised: 60 • Age: NR • Prostate volume (mL) (mean ± SD): 56.81 ± 6.45 • PSA: NR • IPSS (mean ± SD): 21.31 ± 4.04 • Q_{max} (mL/s) (mean ± SD): 10.25 ± 1.34 **Group B** (tamsulosin) • Number of participants randomised: 60 • Age: NR • Prostate volume (mL) (mean ± SD): 57.73 ± 7.33 • PSA: NR • IPSS (mean ± SD): 21.95 ± 4.46 • Q_{max} (mL/s) (mean ± SD): 9.36 ± 1.21
Interventions	**Run-in period:** none **Group A:** naftopidil 75 mg/day **Group B:** tamsulosin 0.4 mg/day **Duration:** 3 months

Griwan 2014 (*Continued*)

Outcomes	**Primary outcomes** • Change from baseline in the total score (questions 1-7) of IPSS, QoL, Q_{max}, prostate volume, PVR • How measured: questionnaire, Q_{max} (Laborie Urocap III uroflowmeter), prostate volume (US), PVR (NR) • Time of measurement: baseline; 1, 3 months • Time of reporting: baseline; 1, 3 months **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none
Funding sources	NR
Declarations of interest	None
Notes	**Language of publication:** English No predefined secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated, simple, randomised analysis" Comment: sequence generation method was provided.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients included in the study as well as the doctor conducting the study were blinded to the drug being administered and the group allocation." Comment: blinding of participants and study personnel ensured
Blinding of outcome assessment (detection bias) Susceptible	Low risk	Quote: "The patients included in the study as well as the doctor conducting the study were blinded to the drug being administered and the group allocation." Comment: blinding of participants and study personnel ensured
Blinding of outcome assessment (detection bias)	Low risk	Comment: objective outcomes not likely affected by lack of blinding

Griwan 2014 (*Continued*)

Not susceptible		
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Quote: "no dropouts during the duration of the study." Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Quote: "no dropouts during the duration of the study." Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Quote: "no dropouts during the duration of the study." Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: study did not address these outcomes.
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Quote: "no dropouts during the duration of the study." Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Quote: "no dropouts during the duration of the study." Comment: all randomised participants were included in analysis
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes were well described but protocol was not published
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias found; therefore, risk of other bias was low

Hanyu 2010

Methods	**Study design:** prospective randomised clinical study **Setting/country:** multicentre (4 centres)/Japan **Study dates:** May 2005 to May 2008
Participants	**Ethnicity:** Japan **Inclusion criteria** • Men aged ≥ 50 years at first visit • Total IPSS ≥ 8, QoL index score ≥ 2 • Prostate volume ≥ 20 mL

	• PVR < 100 mL **Exclusion criteria** • People with prostate cancer, bladder cancer, neurogenic bladder, urethral stricture, or UTI • Administration of hormonal agents for BPH within 1 month before study • Administration of drugs considered to affect urination within 2 weeks before study (e.g. alpha-blocker, beta-blocker, anticholinergic agents, cholinergic agonist, antidepressant) • Serious liver or kidney disorder, cardiac disorder **Total number of participants randomised** • Screened: NR • Eligible: 105 **Group A** (naftopidil) • Number of participants randomised: 55 • Age (years) (mean ± SD): 70.5 ± 5.8 • Prostate volume (mL) (mean ± SD): 40.2 ± 16.3 • PSA: NR • IPSS (mean ± SD): 14.8 ± 5.7 • Q_{max} (mL/s) (mean ± SD): 9.5 ± 3.4 **Group B** (tamsulosin) • Number of participants randomised: 50 • Age (years) (mean ± SD): 70.9 ± 5.8 • Prostate volume (mL) (mean ± SD): 41.0 ± 19.3 • PSA: NR • IPSS (mean ± SD): 13.5 ± 5.0 • Q_{max} (mL/s) (mean ± SD): 8.6 ± 3.5
Interventions	**Run-in period:** none **Group A:** naftopidil 50 mg/day **Group B:** tamsulosin 0.2 mg/day **Duration:** 12 weeks
Outcomes	**Primary outcomes** • IPSS, QoL Index • How measured: questionnaire • Time of measurement: before; 4, 12 weeks • Time of reporting: before; 4, 12 weeks **Secondary outcomes** • Q_{max}, PVR/clinical efficacy evaluated based on IPSS and QoL • How measured: NR/according to "criteria for treatment efficacy in BPH" in the "voiding dysfunction clinical trial guideline" proposed by the Japanese Urological Association • Time of measurement: before; 4, 12 week • Time of reporting: before; 4, 12 weeks **Safety outcome** • Adverse effect • How measured: NR • Time of measurement: NR • Time of reporting: not specified but assumed to be last follow-up (12 weeks)

Hanyu 2010 (*Continued*)

	Subgroup: none	
Funding sources	NR	
Declarations of interest	NR	
Notes	**Language of publication:** Japanese	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random assignment", "using a random number table" Comment: method of random sequence generation had low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 19/55 (34.5%) participants in naftopidil group and 18/50 (36.0%) participants in tamsulosin group were not included in the analysis Owing to a large proportion of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis

Hanyu 2010 (*Continued*)

Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: no cardiovascular adverse events reported in naftopidil group, but 1/40 (2.5%) reported in tamsulosin group Owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: protocol not published.
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias found; therefore, risk of other bias was low

Ikemoto 2003

Methods	**Study design:** randomised cross-over clinical study **Setting/country:** 3 hospitals in single institute/Japan **Study dates:** March 2000 to April 2002
Participants	**Ethnicity:** Japan **Inclusion criteria** • IPSS $\geq$ 8, Q_{max} < 12 mL/s (150 mL voiding) • if prior BPH medication, 1-month washout period **Exclusion criteria:** NR **Total number of participants randomised** • Screened: NR • Eligible: 96 **Group A** (naftopidil) • Number of participants randomised: 43 • Age (years) (mean ± SD): 66.6 ± 7.6 • Prostate volume (mL) (mean ± SD): 38.9 ± 11.8 • PSA: NR • IPSS (mean ± SD): 17.4 ± 6.0 • Q_{max} (mL/s) (mean ± SD): 9.3 ± 4.0 **Group B** (tamsulosin) • Number of participants randomised: 53 • Age (years) (mean ± SD): 63.8 ± 9.1 • Prostate volume (mL) (mean ± SD): 32.7 ± 9.4 • PSA: NR • IPSS (mean ± SD): 16.8 ± 7.2

Ikemoto 2003 (*Continued*)

	• Q_{max} (mL/s) (mean ± SD): 9.1 ± 6.0
Interventions	**Run-in period:** none **Group A:** naftopidil 25 mg/day for first 2 weeks, then 50 mg once daily for 6 weeks then tamsulosin 0.2 mg for 8 weeks **Group B:** tamsulosin 0.2 mg for 8 weeks then naftopidil 25 mg for 2 weeks, then 50 mg for 6 weeks **Duration:** 8 weeks (additional 8 weeks after cross-over/no washout)
Outcomes	**Primary outcomes** • IPSS, QoL, Q_{max}, PVR • How measured: questionnaire, uroflow, abdominal US • Time of measurement: baseline, cross-over, end of treatment • Time of reporting: baseline, cross-over, end of treatment **Secondary outcome** • NR **Safety outcome** • Safety • How measured: questionnaire, uroflowmetry, abdominal US • Time of measurement: NR • Time of reporting: NR **Subgroup:** none
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English No predefined primary or secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly divided with the envelope method" Comment: method of random sequence generation was at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear

Ikemoto 2003 (*Continued*)

Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 12/43 (27.9%) participants in silodosin group and 18/53 (33.9%) participants in naftopidil group not included in analysis Owing to a large proportion of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: protocol not published.
Other bias	Unclear risk	Comment: no washout period

Ju 2002

Methods	**Study design:** double-blind parallel randomised clinical study **Setting/country:** single institute/China **Study dates:** June to November 2011
Participants	**Ethnicity:** NR (China) **Inclusion criteria** • Men aged 50-75 years with BPH • IPSS $\geq$ 13

	• PSA ≤ 4 ng/mL, Q_{max} 5-15 mL/s when urine volume > 150 mL **Exclusion criteria** • Prostate cancer, hypotension, severe heart disease, lung disease, liver diseases, or renal diseases • People who underwent or needed to receive invasive intervention for BPH • Other diseases such as neurogenic bladder, bladder neck obstruction, bladder cancer, benign bladder tumour, bladder diverticular, urethral stricture, or active UTI • Mental disorder • People with poor compliance • Doctor believed person could not take naftopidil **Total number of participants randomised** • Screened: 80 • Eligible: 80 **Group A** (naftopidil) • Number of participants randomised: 40 • Age (years) (mean ± SD): 62.5 ± 5.26 • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 18.79 ± 4.8 • Q_{max} (mL/s) (mean ± SD): 11.24 ± 3.22 **Group B** (tamsulosin) • Number of participants randomised: 40 • Age (years) (mean ± SD): 66.5 ± 5.8 • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 19.71 ± 4.7 • Q_{max} (mL/s) (mean ± SD): 11.32 ± 3.29
Interventions	**Run-in period:** none **Group A:** naftopidil 25 mg once daily **Group B:** tamsulosin 0.2 mg once daily **Duration:** 6 weeks
Outcomes	**Primary outcomes** • IPSS, Q_{max} • How measured: questionnaire, Q_{max} (NR) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, 6 weeks **Secondary outcomes** • QoL, PVR, prostate volume • How measured: questionnaire, PVR (US), prostate volume (US) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, 6 weeks **Safety outcome** • Adverse reactions • How measured: adverse reactions (record) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, 6 weeks **Subgroup:** none

Ju 2002 (*Continued*)

Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** Chinese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes: "double blinded" Comment: no description who was blinded, owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Quotes: "double blinded" Comment: no description who was blinded, owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Comment: 1/40 (2.5%) participants in naftopidil group and 2/40 (5%) participants in tamsulosin group were not included in the analysis, owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear

Ju 2002 (*Continued*)

Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: study did not address this outcome.
Selective reporting (reporting bias)	High risk	Comment: protocol was not published and QoL (secondary outcome) was not reported
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias found; therefore, risk of other bias was low

Kwon 2018

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre/Korea **Study dates:** January 2015 to July 2015
Participants	**Ethnicity:** NR (Korea) **Inclusion criteria** • 94 men who had been taking tamsulosin for > 8 weeks; however, men who persist more than 3 points of OABSS, especially more than 2 points of OABSS question 3 **Exclusion criteria** • Treated with 5-alpha reductase inhibitors within 6 months or anticholinergics within 8 weeks of study commencement • Aged < 40 years, with a lower OABSS after than before treatment • With an abnormal urinalysis (RBC > 5/HPF, WBC > 5/HPF) or liver (an AST/ALT ratio > 100) or renal function (creatinine > 2 mg/dL), or who developed a severe adverse effect during treatment, such as, orthotropic hypotension or an allergic reaction **Total number of participants randomised** • Screened: NR • Eligible: 94 **Group A** (naftopidil) • Number of participants randomised: 49 • Age (years) (mean ± SD): 66.0 ± 6.3 • Prostate volume (mL) (mean ± SD): 36.8 ± 14.6 • PSA: NR • IPSS (mean ± SD): 16.9 ± 6.2 • Q_{max} (mL/s) (mean ± SD): 17.5 ± 25.6 **Group B** (tamsulosin) • Number of participants randomised: 45 • Age (years) (mean ± SD): 64.8 ± 7.7 • Prostate volume (mL) (mean ± SD): 37.5 ± 22.4 • PSA: NR • IPSS (mean ± SD): 19.1 ± 7.2 • Q_{max} (mL/s) (mean ± SD): 15.5 ± 8.4

Kwon 2018 (*Continued*)

Interventions	**Run-in period:** none **Group A:** naftopidil 75 mg/day for 8 weeks **Group B:** tamsulosin 0.2 mg once daily for 8 weeks **Duration:** 8 weeks
Outcomes	**Primary outcomes** • IPSS, OABSS, Q_{max}, PVR • How measured: questionnaires, uroflowmetry, PVR (NR) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, end of treatment **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none
Funding sources	Financial support from Donga ST Pharm Korea, Inc.
Declarations of interest	NR
Notes	**Language of publication:** English No predefined primary or secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-based by randomizations" Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding

Kwon 2018 (*Continued*)

Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: number of participants were not provided or included in analysis, owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: our review outcomes were well described, Author provided raw data but protocol was not published
Other bias	High risk	Quote: "Ninety-four patients that had been taking tamsulosin for more than 8 weeks, however, patients who persist more than 3 points of OABSS, especially more than 2 points of OABSS question 3, were enrolled and divided into two groups." Comment: enrolled participants who had insufficient symptom improvement

Li 2007

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre (9 centre)/China **Study dates:** September 2002 to December 2003
Participants	**Ethnicity:** NR (China) **Inclusion criteria** • Men with BPH/LUTS aged 50-75 years • Total IPSS ≥ 13

	• Prostate volume > 20 mL, Q_{max} < 15 mL/s, PVR < 60 mL **Exclusion criteria** • Other diseases, such as neurogenic bladder, bladder stone, urethral stone, prostate cancer, urethral stricture, or active UTI • Men who underwent or needed to receive invasive intervention for BPH • Severe diabetes, heart disease, lung disease, liver diseases, or renal diseases • Received pharmacological treatment for BPH in past 1 month • Without a history of postural hypotension • Mental disorder **Total number of participants randomised** • Screened: 906 • Eligible: 906 **Group A** (naftopidil) • Number of participants randomised: 126 • Age (years) (mean ± SD): 67.7 ± 5.5 • Prostate volume (mL) (mean ± SD): 38.1 ± 15.4 • PSA (ng/mL) (mean ± SD): 2.5 ± 1.4 • IPSS (mean ± SD): 20.6 ± 5.4 • Q_{max} (mL/s) (mean ± SD): 11.1 ± 3.1 **Group B** (tamsulosin) • Number of participants randomised: 138 • Age (years) (mean ± SD): 66.8 ± 5.4 • Prostate volume (mL) (mean ± SD): 43.1 ± 17.7 • PSA (ng/mL) (mean ± SD): 2.4 ± 1.1 • IPSS (mean ± SD): 21.1 ± 5.6 • Q_{max} (mL/s) (mean ± SD): 10.7 ± 2.8 **Other active:** terazosin; doxazosin; finasteride; epristeride; cernilton
Interventions	**Run-in period:** none **Group A:** naftopidil 25 mg once daily **Group B:** tamsulosin 0.2 mg once daily **Other active:** terazosin 2 mg once daily; doxazosin 4 mg once daily; finasteride 5 mg once daily; epristeride 5 mg twice daily; cernilton 70 mg twice daily **Duration:** 12 months
Outcomes	**Primary outcomes** • IPSS, QoL Index, Q_{max}, PVR • How measured: questionnaire (IPSS, QoL), Q_{max} (NR), PVR (US) • Time of measurement: before; 3, 6, 9, 12 months • Time of reporting: before; 3, 6, 9, 12 months **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none
Funding sources	Chinese National Programs for Science and Technology Development
Declarations of interest	NR

Notes	**Language of publication:** Chinese	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomised, open-label, controlled multicenter study" Comment: open-label trial; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Quote: "randomised, open-label, controlled multicenter study" Comment: open-label trial; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear

Li 2007 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: protocol was not published and QoL (secondary outcome) was not reported
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias found; therefore, risk of other bias was low

Masuda 2012

Methods	**Study design:** randomised cross-over clinical study **Setting/country:** multicentre/Japan **Study dates:** November 2009 to March 2011
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS/BPH, prostate volume ≥ 20 cm^3 • IPSS ≥ 8, QoL score ≥ 3, clinical diagnosis of BPH, aged ≥ 50 years, no prior treatment for BPH **Exclusion criteria** • Organ disorder other than BPH (e.g. prostate cancer, bladder cancer, prostatitis, urethral stricture), previous TURP or minimally invasive treatment, indwelling catheter or urethral self-catheterisation, active UTI, neurogenic cystitis • Nervous system disease as complication • Administration of hormonal agents for BPH within 6 month before study, administration of alpha-blocker within 6 weeks before study, other people deemed unsuitable by attending physician **Total number of participants randomised** • Screened: NR • Eligible: 92 **Group A** (naftopidil) • Number of participants randomised: 48 • Age (years) (mean ± SD): 68.5 ± 5.7 • Prostate volume (mL) (mean ± SD): 45.7 ± 17.8 • PSA: NR • IPSS (mean ± SD): 17.6 ± 5.0 • Q_{max} (mL/s) (mean ± SD): 9.3 ± 4.9 **Group B** (silodosin) • Number of participants randomised: 44 • Age (years) (mean ± SD): 66.5 ± 5.6 • Prostate volume (mL) (mean ± SD): 38.8 ± 13.1 • PSA: NR • IPSS (mean ± SD): 18.6 ± 5.5 • Q_{max} (mL/s) (mean ± SD): 8.0 ± 3.7
Interventions	**Run-in period:** NR **Group A:** naftopidil 50-75 mg once daily for 2 weeks, then 75 mg once daily for 4 weeks **Group B:** silodosin 2-4 mg twice daily for 2 weeks, then 4 mg twice daily for 4 weeks

	Duration: 6 weeks (additional 6 weeks after cross-over, no washout)
Outcomes	**Primary outcome** • IPSS • How measured: questionnaire, uroflowmetry (NR), US (PVR) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, 6 weeks **Secondary outcomes** • IPSS subscore, QoL, OABSS, Q_{max}, PVR, questionnaire to evaluate participant drug preference • How measured: questionnaire, uroflowmetry (NR), US (PVR) • Time of measurement: baseline, 6 weeks • Time of reporting: baseline, 6 weeks **Safety outcome** • Adverse events **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** Japanese This crossover trial had no washout period because authors considered treatment interruption to be disadvantageous to participants. 6 weeks with first drug, followed by another 6 weeks with second drug. Data extracted only from the first period (i.e. at 6 weeks) like a parallel group trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients enrolled consecutively and assigned alternately." Comment: method of random sequence generation at high risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear

Masuda 2012 (*Continued*)

Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 14/48 (29.1%) participants in naftopidil group and 14/44 (31.8%) participants in silodosin group were not included in analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes were well described, but protocol was not published
Other bias	High risk	Comment: drug administration times were different between groups

Masumori 2009

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre (17 centres)/Japan **Study dates:** March 2005 to March 2006
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS/BPH, aged 51-79 years, IPSS ≥ 8 **Exclusion criteria** • History of urinary retention, PVR ≥ 200 mL, hydronephrosis or renal

	impairment caused by bladder outlet obstruction (or both) • Intractable haematuria, prostate cancer, history of prostatic surgery, neurogenic bladder, urethral stricture, and chronic bacterial prostatitis • Receiving alpha-blocker or antiandrogen (or both) in past 3 months **Total number of participants randomised** • Screened: NR • Eligible: 95 **Group A** (naftopidil) • Number of participants randomised: 48 • Age (years) (mean ± SD): 64.5 ± 7.7 • Prostate volume (mL) (mean ± SD): 35.9 ± 15.3 • PSA: NR • IPSS (mean ± SD): 15.0 ± 5.9 • Q_{max} (mL/s) (mean ± SD): 10.7 ± 5.3 **Group B** (tamsulosin) • Number of participants randomised: 47 • Age (years) (mean ± SD): 65.2 ± 7.5 • Prostate volume (mL) (mean ± SD): 34.4 ± 13.7 • PSA: NR • IPSS (mean ± SD): 17.8 ± 5.7 • Q_{max} (mL/s) (mean ± SD): 11.1 ± 4.8
Interventions	**Run-in period:** none **Group A:** naftopidil 50 mg/day **Group B:** tamsulosin 0.2 mg/day **Duration:** 12 weeks
Outcomes	**Primary outcomes** • Incidence of ejaculatory disorders, erectile dysfunction • How measured: questionnaire (evaluate ejaculatory volume), IIEF-5 • Time of measurement: baseline and 12 week • Time of reporting: baseline, 12 weeks **Secondary outcomes** • Q_{max}, PVR, clinical efficacy evaluated based on IPSS and QoL • How measured: IPSS, IPSS-QoL, uroflowmetry (NR), PVR (NR) • Time of measurement: baseline, 12 weeks • Time of reporting: baseline, 12 weeks **Safety outcome** • Adverse events • How measured: NR • Time of measurement: NR • Time of reporting: not specified but assumed to be last follow-up (12 weeks) **Subgroup:** none
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English

Masumori 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "permutated block design" Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 10/48 (20.8%) participants in naftopidil group and 12/47 (25.5%) participants in tamsulosin group were not included in the analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: 3/48 (6%) participants in naftopidil group and 1/47 (2%) participants in tamsulosin group were not included in the analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: 3/48 (6%) participants in the naftopidil group and 1/47 (2%) partici-

Masumori 2009 (*Continued*)

		pants in the tamsulosin group were not included in the analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: 3/48 (6%) participants in the naftopidil group and 1/47 (2%) participants in the tamsulosin group were not included in the analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes are well described, but protocol was not published
Other bias	High risk	Quote: "the IPSS and QOL index at baseline were significantly lower in the naftopidil group than in the tamsulosin group." Comment: baseline imbalance

Matsukawa 2017

Methods	**Study design:** parallel open-label randomised clinical study **Setting/country:** multicentre/Japan **Study dates:** May 2012 to September 2013
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men aged ≥ 50 years • Total IPSS ≥ 8, IPSS-QoL score ≥ 3, total OABSS ≥ 3, ≥ 1 urinary urgency episodes/week • Prostate volume ≥ 20 mL on transabdominal ultrasonography • Q_{max} < 15 mL/s at a voided volume of ≥ 100 mL and PVR < 150 mL **Exclusion criteria** • Received oral treatment with a1-blockers, anticholinergic agents, 5-alpha reductase inhibitors, antidepressants, antianxiety agents, or sex hormonal agents • Neurogenic bladder dysfunction, bladder calculi or active UTI, severe cardiac disease, renal dysfunction (serum creatinine levels ≥ 2 mg/dL) or hepatic dysfunction (AST and ALT concentrations more than twice normal values) • Prostate cancer confirmed by prostate biopsy **Total number of participants randomised** • Screened: 350 • Eligible: 350 **Group A** (naftopidil) • Number of participants randomised: 175 • Age (years) (mean ± SD): 70.3 ± 7.8 • Prostate volume (mL) (mean ± SD): 38.6 ± 14.8

	• PSA (ng/mL) (mean ± SD): 3.0 ± 3.1 • IPSS (mean ± SD): 18.9 ± 6.1 • Q_{max} (mL/s) (mean ± SD): 8.4 ± 3.0 **Group B** (silodosin) • Number of participants randomised: 175 • Age (years) (mean ± SD): 70.6 ± 7.8 • Prostate volume (mL) (mean ± SD): 39.6 ± 16.7 • PSA (ng/mL) (mean ± SD): 3.0 ± 3.1 • IPSS (mean ± SD): 18.8 ± 6.2 • Q_{max} (mL/s) (mean ± SD): 8.2 ± 3.6
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg/day for 4 weeks, then 75 mg/day for 8 weeks **Group B:** silodosin 4 mg/day for 4 weeks, then 8 mg/day for 8 weeks **Duration:** 12 weeks
Outcomes	**Primary outcomes** • IPSS, QoL Index, OABSS • How measured: questionnaire • Time of measurement: baseline; 4, 12 weeks • Time of reporting: baseline; 4, 12 weeks **Secondary outcomes** • Q_{max}, PVR • How measured: uroflowmetry, PVR (NR) • Time of measurement: baseline; 4, 12 weeks • Time of reporting: baseline; 4, 12 weeks **Safety outcome** • Adverse reactions • How measured: NR • Time of measurement: NR • Time of reporting: NR **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomizations using a random number table at the study center." Comment: method of random sequence generation at low risk of bias

Matsukawa 2017 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, open label, randomised, multicenter study." Comment: open-label trial; no blinding; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Susceptible	Low risk	Quote: "The data obtained were de-identified and analysed independently by 2 of our research group members not involved in this study." Comment: open-label trial; no blinding; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: 18/175 (10.2%) participants in naftopidil group and 18/175 (10.2%) participants in silodosin group were not included in analysis but missing outcome data balanced in numbers across intervention groups with similar reasons Owing to the moderated number of participants lost to follow-up (> 10%), risk of attrition bias was low
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all participants were enrolled in analysis.
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all participants were enrolled in analysis.
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all participants were enrolled in analysis.
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear

Matsukawa 2017 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes are well described, but protocol was not published
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Momose 2007

Methods	**Study design:** cross-over randomised clinical study **Setting/country:** single centre/Japan **Study dates:** February 2002 to December 2003
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS with BPH **Exclusion criteria** • Drugs that might affect urinary excretion function, prostate cancer, neurogenic bladder suspected, UTI, chronic bacterial prostatitis, etc. **Total number of participants randomised** • Screened: NR • Eligible: 45 **Group A** (naftopidil) • Number of participants randomised: 20 • Age (years) (mean ± SD): 65.3 ± 5.5 • Prostate volume (mL) (mean ± SD): 30.7 ± 13.8 • PSA: NR • IPSS (mean ± SD): 19.6 ± 7.0 • Q_{max} (mL/s) (mean ± SD): 9.4 ± 3.2 **Group B** (tamsulosin) • Number of participants randomised: 25 • Age (years) (mean ± SD): 68.2 ± 7.7 • Prostate volume (mL) (mean ± SD): 47.2 ± 22.6 • PSA: NR • IPSS (mean ± SD): 18.4 ± 6.9 • Q_{max} (mL/s) (mean ± SD): 9.2 ± 3.3
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg/day for 4 weeks, then tamsulosin 0.2 mg/day for 4 weeks **Group B:** tamsulosin 0.2 mg/day for 4 weeks, then naftopidil 50 mg/day for 4 weeks **Duration:** 28 days (additional 28 days after cross-over/no washout)
Outcomes	**Primary outcomes** • Total IPSS, storage symptoms, voiding symptoms, QoL score • How measured: questionnaire • Time of measurement: baseline; 4, 8 weeks • Time of reporting: baseline; 4, 8 weeks

	Secondary outcome • NR **Safety outcome** • Safety • How measured: NR • Time of measurement: NR • Time of reporting: NR **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English No predefined primary and secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis

Momose 2007 (*Continued*)

Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes were well described, but protocol was not published
Other bias	Unclear risk	Comment: no washout period

Nishino 2006

Methods	**Study design:** cross-over randomised clinical study **Setting/country:** single centre/Japan **Study dates:** NR
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS secondary to BPH **Exclusion criteria** • Total IPSS < 7 or Q_{max} >15 mL/s • Neurogenic disorders, UTI, urinary retention, bladder tumour, or bladder stones **Total number of participants randomised** • Screened: NR • Eligible: 34 **Group A** (naftopidil) • Number of participants randomised: 17 • Age (years) (mean ± SD): 73.2 ± 4.1 • Prostate volume (mL) (mean ± SD): 20.6 ± 3.7 • PSA: NR • IPSS (mean ± SD): 20.7 ± 4.3 • Q_{max} (mL/s) (mean ± SD): 9.7 ± 0.4 **Group B** (tamsulosin) • Number of participants randomised: 17 • Age (years) (mean ± SD): 71.5 ± 4.5 • Prostate volume (mL) (mean ± SD): 18.9 ± 2.8 • PSA: NR • IPSS (mean ± SD): 20.1 ± 2.7 • Q_{max} (mL/s) (mean ± SD): 10.1 ± 0.7

Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg/day for 4 weeks, then tamsulosin 0.2 mg/day for 4 weeks **Group B:** tamsulosin 0.2 mg/day for 4 weeks, then naftopidil 50 mg/day for 4 weeks **Duration:** 4 weeks: data analysis (4 weeks before cross-over, 1-week washout, and additional 4 weeks after cross-over)
Outcomes	**Primary outcomes** • Improvement in LUTS and QoL, values of uroflowmetry, and PFS • How measured: IPSS questionnaire, uroflowmetry, and PFS • Time of measurement: baseline, 8 weeks • Time of reporting: baseline, 8 weeks **Secondary outcome** • NR **Safety outcome** • Adverse events • How measured: NR • Time of measurement: NR • Time of reporting: NR **Subgroup:** NR
Funding sources	Gifu University, Japan
Declarations of interest	None
Notes	**Language of publication:** English No predefined primary and secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no description who was blinded, owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Quote: "double-blind" Comment: no description who was blinded, owing to insufficient information, risk of performance bias was unclear

Nishino 2006 (*Continued*)

Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: all randomised participants were included in analysis
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes are well described, but protocol was not published
Other bias	Low risk	Comment: 1-week washout period.

Perumal 2015

Methods	**Study design:** prospective parallel randomised **Setting/country:** single centre/India **Study dates:** September 2011 to June 2013
Participants	**Ethnicity:** NR (India) **Inclusion criteria** • Men aged > 50 years, clinical symptoms of BPE, LUTS, with or without raised PVR urine **Exclusion criteria** • Untreated UTI, palpable nodule in the prostate, associated upper urinary tract changes and prostate size > 60 mL **Total number of participants randomised** • Screened: NR • Eligible: 60 **Group A** (naftopidil) • Number of participants randomised: 30 • Age (years) (mean ± SD): 59.9 ± 5.5

	• prostate volume: NR • PSA: NR • IPSS (mean ± SD): 19.97 ± 2.53 • Q_{max} (mL/s) (mean ± SD): 8.63 ± 1.38 **Group B** (tamsulosin) • Number of participants randomised: 30 • Age (years) (mean ± SD): 60.1 ± 5.0 • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 21.3 ± 2.84 • Q_{max} (mL/s) (mean ± SD): 8.37 ± 1.22
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg once daily **Group B:** tamsulosin 0.4 mg once daily **Duration:** 30 days
Outcomes	**Primary outcomes** • IPSS, Q_{max}, PVR • How measured: questionnaire, uroflowmetry (Q_{max}), abdominal US • Time of measurement: baseline, 15/30 days • Time of reporting: baseline, 15/30 days **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** NR
Funding sources	Mahatma Gandhi Medical College and Research Institute
Declarations of interest	None
Notes	**Language of publication:** English No predefined secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "who presented on odd numbered days were placed in Group A, patients who presented on even number days were placed in study Group B." Comment: method of random sequence generation at high risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear

Perumal 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: adverse events were not reported and protocol was not published
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Shirakawa 2013

Methods	**Study design:** randomised, open-label, controlled **Setting/country:** Kobe University School or other collaborating institutions/Japan **Study dates:** July 2007 to March 2011
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with BPH/LUTS, total IPSS 8 points, QoL index 3 points, Q_{max} < 15 mL/s, prostate volume 20 mL • Men with BPH/LUTS without history of using any alpha blocker (hereafter, drug-naive group) or men with BPH/LUTS who had continued to use tamsulosin 0.2 mg once daily for at least 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 tumour, cystolithiasis, prostatitis, urethral stricture, or active UTI • Complication of neurogenic bladder or disease suspected of neurogenic bladder • Participation in study deemed inappropriate by their primary physician **Total number of participants randomised** • Screened: NR • Eligible: 121 **Group A** (naftopidil) • Number of participants randomised: 60 • Age (years) (mean ± SD): 70.50 ± 6.58 • Prostate volume (mL) (mean ± SD): 39.39 ± 25.96 • PSA: NR • IPSS (mean ± SD): 17.56 ± 6.73 • Q_{max} (mL/s) (mean ± SD): 11.13 ± 6.53 **Group B** (silodosin) • Number of participants randomised: 61 • Age (years) (mean ± SD): 70.98 ± 6.69 • Prostate volume (mL) (mean ± SD): 38.24 ± 12.94 • PSA: NR • IPSS (mean ± SD): 17.53 ± 5.4 • Q_{max} (mL/s) (mean ± SD): 9.87 ± 4.50
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg once daily **Group B:** silodosin 4 mg twice daily **Duration:** 8 consecutive weeks
Outcomes	**Primary outcomes** • Total IPSS, subtotal IPSS of storage symptoms, subtotal IPSS of voiding symptoms, postmicturition symptoms, QoL index • How measured: IPSS questionnaire • Time of measurement: baseline; 4, 8 weeks • Time of reporting: baseline; 4, 8 weeks **Secondary outcome** • NR **Safety outcome** • Safety

	• How measured: adverse events • Time of measurement: NR • Time of reporting: NR **Subgroup** • Drug-naive/drug-switching
Funding sources	NR
Declarations of interest	None
Notes	**Language of publication:** English No predefined primary, secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned, using a random number table" Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomised, open-label, controlled multicenter study" Comment: open-label trial; no blinding; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Susceptible	High risk	Quote: "randomised, open-label, controlled multicenter study" Comment: open-label trial; no blinding; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Comment: 4/60 (6.7%) participants in naftopidil group and 5/61 (8.2%) participants in silodosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low

Shirakawa 2013 (*Continued*)

Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: 3/60 (5.0%) participants in naftopidil group and 2/61 (3.3%) participants in silodosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: 3/60 (5.0%) participants in naftopidil group and 2/61 (3.3%) participants in silodosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: 3/60 (5.0%) participants in naftopidil group and 2/61 (3.3%) participants in silodosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Selective reporting (reporting bias)	Low risk	Comment: protocol (UMIN000008331) was published. While results were shown separately in participants with drug naive and switching group, review outcomes were well described
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Singh 2013

Methods	**Study design:** prospective parallel randomised clinical study **Setting/country:** single institution/India **Study dates:** October 2010 to April 2012
Participants	**Ethnicity:** NR (India) **Inclusion criteria** • Men with BPH with IPSS > 8 or > 3 points for frequency, nocturia, and urgency on IPSS • Prostate volume > 15 mL, or peak flow rate < 10 mL for a voided volume > 150 mL **Exclusion criteria** • Hypersensitivity to alpha-blockers; history of prostatic or urethral surgery; men with absolute indications for prostate surgery • Neurological disorders; neurogenic bladder; and cardiovascular, renal, or hepatic dysfunction **Total number of participants randomised** • Screened: NR • Eligible: 110 **Group A** (naftopidil) • Number of participants randomised: 55 • Age (years) (mean): 61.69 • Prostate volume (mL) (mean): 31.38 • PSA: NR • IPSS (mean): 21.06 • Q_{max} (mL/s) (mean): 10.62 **Group B** (tamsulosin) • Number of participants randomised: 55 • Age (years) (mean): 61.15 • Prostate volume (mL) (mean): 30.01 • PSA: NR • IPSS (mean): 21.53 • Q_{max} (mL/s) (mean): 9.41
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg once daily **Group B:** tamsulosin 0.4 mg once daily **Duration:** 12 weeks
Outcomes	**Primary outcomes** • IPSS, Q_{max}, PVR, mean flow rate • How measured: questionnaire, uroflowmetry, US • Time of measurement: baseline; 2, 4, 6, 12 weeks • Time of reporting: baseline; 2, 4, 6, 12 weeks **Secondary outcome** • NR **Safety outcome** • Adverse effects • How measured: NR • Time of measurement: NR

	• Time of reporting: NR **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised per a randomizations table generated." Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: personnel were blinded but the study did not address the blind of participants
Blinding of outcome assessment (detection bias) Susceptible	Low risk	Quote: "The randomizations/allocation of patient group(s) and patient data per protocol was recorded by a resident (second author) who was blinded to the study medication. The protocol, concept, design, and intellectual content for the current study was drafted, conceived, and contributed by the first author who was also blinded to relevant patient data at the time of its interpretation and statistical analysis." Comment: risk of detection bias was low.
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Comment: 5/55 (9.0%) participants in naftopidil group and 4/55 (7.2%) participants in tamsulosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low

Singh 2013 (*Continued*)

Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Low risk	Comment: 5/55 (9.0%) participants in naftopidil group and 4/55 (7.2%) participants in tamsulosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: 5/55 (9.0%) participants in naftopidil group and 4/55 (7.2%) participants in tamsulosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: 5/55 (9.0%) participants in naftopidil group and 4/55 (7.2%) participants in tamsulosin group were not included in analysis Owing to the small number of participants lost to follow-up, risk of attrition bias was low
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes are well described, but protocol was not published
Other bias	Low risk	Study appeared free of other source. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Ub 2016

Methods	**Study design:** randomised cross-over study **Setting/country:** multicentre/Japan **Study dates:** December 2009 to March 2013
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with OAB and BPH who met the following criteria and not administered medication (except herbal preparation) for urinary disorder: IPSS ≥ 2, QoL score ≥ 2,

	OABSS ≥ 3 (urgency score ≥ 2) **Exclusion criteria** • History of hypersensitivity to naftopidil, tamsulosin, or solifenacin • Angle-closure glaucoma • Pylos, duodenum or bowel obstruction, or paralytic ileus, gastric atony, or intestinal atony • Severe myasthenia, serious cardiac disease, severe hepatic dysfunction (Child-Pugh classification C), Parkinson's disease **Total number of participants randomised** • Screened: NR • Eligible: 59 **Group A** (naftopidil) • Number of participants randomised: NR • Age (years) (mean ± SD): 74.7 ± 8.0 • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 17.4 ± 6.7 • Q_{max}: NR **Group B** (tamsulosin) • Number of participants randomised: NR • Age (years) (mean ± SD): 71.9 ± 8.3 • Prostate volume: NR • PSA: NR • IPSS (mean ± SD): 18.1 ± 5.4 • Q_{max}: NR
Interventions	**Run-in period:** NR **Group A:** naftopidil 75 mg/day **Group B:** tamsulosin 0.2 mg/day + solifenacin 5 mg/day **Duration:** 8 weeks (additional 8 weeks after cross-over, no washout: authors judged that evaluation without washout period would be feasible)
Outcomes	**Primary outcomes** • IPSS, QoL index, OABSS, PVR, voided volume, Q_{max}, participant questionnaire (which drug participant preferred with reason) • How measured: questionnaire, uroflowmetry where possible • Time of measurement: 8 weeks, Q_{max} (whenever possible) • Time of reporting: baseline, 8 weeks (16 weeks reported but not extracted; see note) **Secondary outcome** • NR • How measured: NR • Time of measurement: NR • Time of reporting: baseline, 8 weeks (16 weeks reported but not extracted; see note) **Safety outcome** • Adverse effect • How measured: NR • Time of measurement: NR

	• Time of reporting: baseline, 8 weeks (16 weeks reported but not extracted; see note) **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** Japanese **Reason for why data was not extracted:** This cross-over trial had no washout period because authors judged that evaluation without washout period would be feasible This cross-over trial did not report data on the within-person differences (paired analysis) . 59 were randomised, of whom 28 dropped out. 5 withdrew due to participant's own reason; 12 not eligible (excluded after randomisation); 8 withdrew due to adverse effects; 3 withdrew due to lack of improvement or symptom getting worse

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "envelope method" Comment: method of allocation concealment at low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "comparison of 1 tablet and 2 tablets" Comment: participants may have known which medication they are taking therefore risk of performance bias was high
Blinding of outcome assessment (detection bias) Susceptible	High risk	Quote: "comparison of 1 tablet and 2 tablets" Comment: study did not address blinding of personnel but assume not done; therefore, risk of detection bias was high
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 28/59 (47%) participants were not included in the analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high

Ub 2016 (*Continued*)

Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: not available (cross-over trial)
Incomplete outcome data (attrition bias) Cardiovascular adverse events	High risk	Comment: 28/59 (47%) participants were not included in the analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Sexual adverse events	High risk	Comment: 28/59 (47%) participants were not included in the analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Selective reporting (reporting bias)	Unclear risk	Comment: results section stated that uroflowmetry data were dropped from treatment efficacy analysis due to large amount of missing data and protocol was not published
Other bias	Unclear risk	Comment: no washout period

Ukimura 2008

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre/Japan **Study dates:** June 2004 to July 2007
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men aged ≥ 50 years, number of nocturia ≥ 2 • IPSS ≥ 8, QoL index ≥ 3 • Residual urine volume < 50 mL (evaluated by US estimation) • Maximum voiding flow rate < 15 mL/s (preferably with a urination volume ≥ 150 mL) • Prostate volume < 50 mL **Exclusion criteria** • Prostate cancer, acute prostatitis, or narrowing of the urinary tract • Received prostate surgery, balloon dilation, urinary tract stenting, hyperthermia, or pelvic radiation before beginning of study

	• Catheterised or were performing intermittent self-catheterisation • Marked night-time polyuria • Active UTI (urinary WBC count ≥ 5/HPF) • Suspected to have neurogenic bladder or other neurological disorders • Severe ischaemic heart disease, cerebrovascular disorders, liver dysfunction, or kidney dysfunction • Hypotension (systolic BP ≤ 100 mmHg and diastolic BP ≤ 60 mmHg), orthostatic hypotension, or severe hypertension • Hypersensitivity to naftopidil or tamsulosin • Administered a hormonal drug for prostatic hyperplasia within 1 month prior to the beginning of study • Administered a drug that might affect urination other than hormonal drugs for the treatment of prostatic hyperplasia within 2 weeks prior to the beginning of study • Judged by the attending physicians to be inappropriate as participants. **Total number of participants randomised** • Screened: NR • Eligible: 81 **Group A** (naftopidil) • Number of participants randomised: NR • Age (years) (mean ± SD): 69.6 ± 6.8 • Prostate volume (mL) (mean ± SD): 24.4 ± 6.9 • PSA: NR • IPSS (mean ± SD): 17.2 ± 6.4 • Q_{max} (mL/s) (mean ± SD): 9.9 ± 5.5 **Group B** (tamsulosin) • Number of participants randomised: NR • Age (years) (mean ± SD): 68.8 ± 8.2 • Prostate volume (mL) (mean ± SD): 26.7 ± 7.9 • PSA: NR • IPSS (mean ± SD): 18.9 ± 6.6 • Q_{max} (mL/s) (mean ± SD): 9.6 ± 4.8
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg once daily **Group B:** tamsulosin 0.2 mg once daily **Duration:** 6-8 weeks
Outcomes	**Primary outcomes** • IIPSS, QoL, urination volume, Q_{max}, mean flow rate (Q_{mean}), residual urine volume, and urination time • How measured: questionnaire, uroflowmetry • Time of measurement: baseline; 2, 6-8 weeks • Time of reporting: baseline; 2, 6-8 weeks **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** NR

Ukimura 2008 (*Continued*)

Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "birthday was an odd number," "birthday was an even number" Comment: method of random sequence generation at high risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 22/81 (24.7%) participants were not included in the analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear

Ukimura 2008 (*Continued*)

Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: protocol was not published and Adverse events were not addressed
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Yamaguchi 2013

Methods	**Study design:** parallel randomised clinical study **Setting/country:** multicentre/Japan **Study dates:** December 2007 to November 2010
Participants	**Ethnicity:** Japan **Inclusion criteria** • Men with BPH aged ≥ 50 years • Significant LUTS and deteriorated QoL • IPSS ≥ 8 and QoL score ≥ 3 **Exclusion criteria** • Established prostate cancer • Neurogenic bladder and any other complications that affect micturitional status • Men who underwent prostate surgery, intervention, or radiotherapy **Total number of participants randomised** • Screened: 109 • Eligible: 109 **Group A** (naftopidil) • Number of participants randomised: 51 • Age (years) (mean ± SD): 70.0 ± 7.0 • Prostate volume (mL) (mean ± SD): 39.5 ± 18.0 • PSA (ng/mL) (mean ± SD): 3.9 ± 3.5 • IPSS (mean ± SD): 18.9 ± 7.0 • Q_{max} (mL/s) (mean ± SD): 9.9 ± 5.3 **Group B** (tamsulosin) • Number of participants randomised: 58 • Age (years) (mean ± SD): 69.3 ± 7.8 • Prostate volume (mL) (mean ± SD): 33.2 ± 21.2 • PSA (ng/mL) (mean ± SD): 2.8 ± 3.3 • IPSS (mean ± SD): 16.9 ± 5.5 • Q_{max} (mL/s) (mean ± SD): 10.4 ± 5.0

Yamaguchi 2013 (*Continued*)

Interventions	**Run-in period:** none **Group A:** naftopidil 75 mg/day **Group B:** silodosin 8 mg/day **Duration:** 12 weeks
Outcomes	**Primary outcomes** • IPSS, QoL Index, IIEF-5, Q_{max} (mL/s), PVR (mL) • How measured: questionnaire, uroflowmetry, PVR (NR) • Time of measurement: before; 4, 8, 12 weeks after treatment • Time of reporting: IPSS, QoL, IIEF: before; 4, 8, 12 weeks after treatment; Q_{max}, PVR: before; 12 weeks after treatment **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none
Funding sources	NR
Declarations of interest	None
Notes	**Language of publication:** English No predefined primary, secondary outcomes 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	Quote: "random number table envelope method" Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of detection bias was unclear

Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	High risk	Comment: 13/51 (25.5%) participants in naftopidil group and 17/58 (29.3%) participants in silodosin group were not included in analysis Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was high
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants 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	Comment: all randomised participants were included in analysis We received the data after contacting the study author
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Low risk	Comment: all randomised participants were included in analysis We received the data after contacting the study author.
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Low risk	Comment: all randomised participants were included in analysis We received the data after contacting the study author.
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: all sexually active participants (21/44 (47%) participants in naftopidil group; 23/53 (44%) participants in silodosin group) who were randomised were included in analysis
Selective reporting (reporting bias)	Unclear risk	Comment: data (treatment withdrawal, AUR, and surgical intervention) were given by contact with study author, but protocol was not published
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Yamanishi 2004

Methods	**Study design:** single-blind, randomised parallel clinical study **Setting/country:** single centre/Japan **Study dates:** NR
Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • IPSS ≥ 8, Q_{max} < 12 mL/s, prostate volume ≥ 15 mL • Obstructive (or equivocal) condition on International Continence Society nomogram as assessed in a pressure/flow study. **Exclusion criteria** • Complete urinary retention • Prostatic cancer, prostatitis, and urethral stricture • Severe cardiac or cerebrovascular disorders, hepatic disorders, renal dysfunction, or orthostatic hypotension • Medication with anticholinergics, other ABs, beta-agonists, or beta-antagonists **Total number of participants randomised** • Screened: NR • Eligible: 49 **Group A** (naftopidil) • Number of participants randomised: 36 • Age (years) (mean ± SD): 67.5 ± 8.2 • Prostate volume (mL) (mean ± SD): 29.7 ± 14.9 • PSA: NR • IPSS (mean ± SD): 15.4 ± 5.7 • Q_{max} (mL/s) (mean ± SD): 9.8 ± 4.4 **Group B** (Eviprostat) • Number of participants randomised: 13 • Age (years) (mean ± SD): 69.0 ± 6.5 • Prostate volume (mL) (mean ± SD): 29.5 ± 15.9 • PSA: NR • IPSS (mean ± SD): 16.0 ± 6.9 • Q_{max} (mL/s) (mean ± SD): 8.5 ± 4.4
Interventions	**Run-in period:** 1 weeks **Group A:** naftopidil 25 mg once daily for 2 weeks, then 50 mg once daily for 2 weeks, and then 75 mg once daily for 2 weeks **Group B:** Eviprostat 6 tablets daily **Duration:** 6 weeks
Outcomes	**Primary outcomes** • IPSS, QoL, Q_{max}, PVR, urodynamic parameters • How measured: questionnaire, uroflowmetry, catheterisation, video-urodynamic studies • Time of measurement: baseline, 4-6 weeks (endpoint) • Time of reporting: baseline, 4-6 weeks (endpoint) **Secondary outcome** • NR **Safety outcome** • NR **Subgroup:** none

Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English No predefined primary or secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "using an envelope indicating one of the two groups." Comment: method of random sequence generation at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind, randomised controlled study." Comment: no description who was blinded, single blinding; therefore, risk of performance bias was high
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Quote: "single-blind, randomised controlled study" Comment: no description who was blinded, single blinding; therefore, risk of detection bias was high
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis

Yamanishi 2004 (*Continued*)

Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: protocol was not published.
Other bias	Unclear risk	Comment: "observation run-in period of 1 week"

Yokoyama 2009

Methods	**Study design:** prospective randomised controlled clinical study **Setting/country:** 2 centres/Japan **Study dates:** June 2004 to March 2007
Participants	**Ethnicity:** NR/Japan **Inclusion criteria** • Men aged ≥ 50 years • IPSS ≥ 8, 2-day frequency volume chart showing ≥ 1 episode/day of urinary urgency • Daytime voiding frequency ≥ 8 episodes/day, night-time voiding frequency ≥ 1 episode/night • PVR ≤ 50 mL • Men with elevated serum PSA level (> 10 ng/mL) were confirmed as having BPH before the treatment by transrectal US-guided prostate sextant biopsies **Exclusion criteria:** NR **Total number of participants randomised** • Screened: NR • Eligible: 58 **Group A** (naftopidil) • Number of participants randomised: 19 • Age (years) (mean ± SD): 69.1 ± 8.3 • Prostate volume (mL) (mean ± SD): 26.6 ± 12.3 • PSA: NR • IPSS (mean ± SD): 18.2 ± 5.7 • Q_{max} (mL/s) (mean ± SD): 9.8 ± 4.0 **Group B** (propiverine hydrochloride) • Number of participants randomised: 18 • Age (years) (mean ± SD): 70.9 ± 6.7 • Prostate volume (mL) (mean ± SD): 25.3 ± 7.7

Yokoyama 2009 (*Continued*)

	• PSA: NR • IPSS (mean ± SD): 18.2 ± 7.0 • Q_{max} (mL/s) (mean ± SD): 9.5 ± 3.1
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg/day **Group B:** propiverine hydrochloride 20 mg/day **Group C:** naftopidil 50 mg/day + propiverine hydrochloride 20 mg/day **Duration:** 4 weeks
Outcomes	**Primary outcomes** • IPSS, QoL Index, urinary urgency, voiding frequency, daily void volume, urinary urgency, urinary incontinence, Q_{max}, PVR • How measured: questionnaire, Urgency Perception Scale, frequency volume charts, uroflowmetry, transabdominal ultrasonography • Time of measurement: before, 4 weeks • Time of reporting: before, 4 weeks **Secondary outcome** • NR **Safety outcome** • Safety • How measured: NR • Time of measurement: NR • Time of reporting: NR **Subgroup:** NR
Funding sources	NR
Declarations of interest	None
Notes	**Language of publication:** English 3-arm comparison: naftopidil vs propiverine versus naftopidil + propiverine (not eligible for our review) No predefined primary or secondary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Comment: owing to insufficient information, risk of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear

Yokoyama 2009 (*Continued*)

Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: owing to insufficient information, risk of performance bias was unclear
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: 8/66 (12.1%) randomised participants were not included in analysis Owing to moderate number of participants lost to follow-up (> 10%), risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Unclear risk	Comment: owing to insufficient information to permit judgement, risk of attrition bias was unclear
Selective reporting (reporting bias)	Unclear risk	Comment: protocol was unpublished.
Other bias	Low risk	Study appeared free of other sources of bias. Comment: no other sources of bias could be found; therefore, risk of other bias was low

Yokoyama 2011

Methods	**Study design:** parallel randomised clinical study **Setting/country:** 2 centres/Japan **Study dates:** NR

Yokoyama 2011 (*Continued*)

Participants	**Ethnicity:** NR (Japan) **Inclusion criteria** • Men with LUTS aged 50-80 years, IPSS ≥ 8 **Exclusion criteria** • Received oral treatment with 5-alpha reductase inhibitors, anticholinergic drugs, antidepressants, or sex hormonal drugs • Neurogenic bladder dysfunction, bladder calculi, or active UTI, or had severe cardiac disease, renal dysfunction (serum creatinine > 2 mg/dL), or hepatic dysfunction. **Total number of participants randomised** • Screened: 136 • Eligible: 136 **Group A** (naftopidil) • Number of participants randomised: 46 • Age (years) (mean ± SD): 69.1 ± 1.2 • Prostate volume (mL) (mean ± SD): 35.0 ± 3.1 • PSA: NR • IPSS (mean ± SD): 17.4 ± 0.8 • Q_{max} (mL/s) (mean ± SD): 8.63 ± 0.5 **Group B** (tamsulosin) • Number of participants randomised: 45 • Age (years) (mean ± SD): 71.5 ± 1.1 • Prostate volume (mL) (mean ± SD): 32.5 ± 2.0 • PSA: NR • IPSS (mean ± SD): 18.0 ± 1.1 • Q_{max} (mL/s) (mean ± SD): 8.56 ± 0.5 **Group C** (silodosin) • Number of participants randomised: 45 • Age (years) (mean ± SD): 70.2 ± 0.9 • Prostate volume (mL) (mean ± SD): 33.3 ± 2.3 • PSA: NR • IPSS (mean ± SD): 18.7 ± 0.7 • Q_{max} (mL/s) (mean ± SD): 9.03 ± 0.6
Interventions	**Run-in period:** NR **Group A:** naftopidil 50 mg once daily **Group B:** tamsulosin 0.2 mg once daily **Group C:** silodosin 4 mg twice daily **Duration:** 12 weeks
Outcomes	**Primary outcomes** • IPSS, QoL Index, IIEF-5, ejaculation, Q_{max}, PVR • How measured: questionnaire, ultrasonography (PVR), uroflowmetry (NR) • Time of measurement: before; 1, 3 months after treatment ended • Time of reporting: before; 1, 3 months after treatment ended **Secondary outcome** • NR **Safety outcome** • Safety • How measured: NR

	• Time of measurement: NR • Time of reporting: NR **Subgroup:** NR
Funding sources	NR
Declarations of interest	NR
Notes	**Language of publication:** English No predefined primary or secondary outcomes, data (IPSS, QoL, AUR, and surgical intervention) from study author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomly assigned" Comment: study author reply, "Computer generated central randomization"
Allocation concealment (selection bias)	Low risk	Comment: study author reply, "Computer generated central randomization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: study author reply, "participants were not blinded"
Blinding of outcome assessment (detection bias) Susceptible	Unclear risk	Comment: study did not address this outcome.
Blinding of outcome assessment (detection bias) Not susceptible	Low risk	Comment: objective outcomes not likely affected by lack of blinding
Incomplete outcome data (attrition bias) IPSS/QoL	Unclear risk	Comment: 14/136 (10.2%) participants who were randomised were not included in analyses owing to the moderate number of participants lost to follow-up (> 10%), risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Treatment withdrawal for any reason	Low risk	Comment: all randomised participants were included in analysis
Incomplete outcome data (attrition bias) Treatment withdrawal due to adverse events	Unclear risk	Comment: 14/136 (10.2%) participants who were randomised were not included in analyses Owing to the moderate number of partici-

Yokoyama 2011 (*Continued*)

		pants lost to follow-up (> 10%), risk of attrition bias was unclear
Incomplete outcome data (attrition bias) AUR/Surgical intervention	Unclear risk	Comment: 14/136 (10.2%) participants who were randomised were not included in analyses Owing to the moderate number of participants lost to follow-up (> 10%), risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Cardiovascular adverse events	Unclear risk	Comment: 14/136 (10.2%) participants who were randomised were not included in analyses Owing to the moderate number of participants lost to follow-up (> 10%), risk of attrition bias was unclear
Incomplete outcome data (attrition bias) Sexual adverse events	Low risk	Comment: analyses limited to men who were sexually active (15/46 (32.6%) participants in naftopidil group, 17/45 (37.8%) participants in tamsulosin group, 17/45 (37.7%) participants in silodosin group; all sexually active) All participants were included in analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: protocol was not published.
Other bias	High risk	Comment: drug administration times were different between group. Baseline imbalance in PVR; silodosin group had much higher PVR, which may have underestimated the effect size

AB: alpha blocker; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUR: acute urinary retention; BP: blood pressure; BPE: benign prostatic enlargement; BPH: benign prostatic hyperplasia; CI: confidence interval; HPF: high power field; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; IPSS-QoL: International Prostate Symptom Score - Quality of Life; LUTS: lower urinary tract infection; NR: not reported; OAB: overactive bladder; OABSS: Overactive Bladder Symptom Score; PFS: pressure flow study; PSA: prostate-specific antigen; PVR: postvoid residual; QoL: quality of life; Q_{max}: maximal flow rate; RBC: red blood cell; s: second; TURP: transurethral resection of prostate; US: ultrasound; UTI: urinary tract infection; VAS: visual analogue scale; WBC: white blood cell.

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

Study	Reason for exclusion
Carson 2017	Commentary
Hayashi 2002	Ineligible study design (non-randomised trial)
Hiroshi 2011	Ineligible comparator (naftopidil 25 mg vs 50 mg vs 75 mg)
Ikemoto 2010	Review
Maruyama 2006	Ineligible comparator (naftopidil 25-75 mg vs naftopidil 25-75 mg + oxybutynin hydrochloride 4-8 mg or naftopidil 25-75 mg + propiverine hydrochloride 10-20 mg)
Sakai 2011	Ineligible comparator (naftopidil 50 mg morning medication vs naftopidil 50 mg evening medication)
Tsuritani 2010	Ineligible comparator (naftopidil 75 mg once daily in the evening vs 25 mg 3 times daily)
Yamaguchi 1992	Ineligible outcomes (symptom improvement rates, outcome not measured)
Yamaguchi 1997	Ineligible outcomes (symptom improvement rates, outcome not measured)
Yokoyama 2006	Ineligible comparator (naftopidil 75 mg/day vs 25 mg/day)

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

NCT01203371

Methods	Randomised, double-blind, parallel group design
Participants	**Inclusion criteria** • Aged 50-90 years • Signs and symptoms of BPH • IPSS ≥ 10 • Prostate volume ≥ 20 mL • PVR > 150 mL **Exclusion criteria** • History of allergy to an alpha-blocker • Treatment with antiandrogen drugs • Drugs with anticholinergic activity • Significant history of orthostatic hypotension • Concomitant neurological diseases • Known or suspected neurogenic bladder dysfunction • Carcinoma of prostate or bladder • Previous surgery for BPH or bladder neck obstruction • History of recurrent UTI • Concomitant active UTI

NCT01203371 (*Continued*)

Interventions	**Group A:** naftopidil 25 mg for 2 weeks then 50 mg for 10 weeks **Group B:** tamsulosin 0.4 mg/day for 12 weeks
Outcomes	**Primary outcome** • IPSS (2, 4, 8, 12 weeks) **Secondary outcome** • Adverse effect (2, 4, 8, 12 weeks)
Notes	**Funding sources:** Apsen Farmaceutica S.A. **Publication status:** NCT01203371 (final publication status has not been clarified)

NCT01922375

Methods	Placebo-controlled, randomised, double-blind, double-dummy, parallel-group, fixed-dose design
Participants	**Inclusion criteria** • Aged ≥ 45 years with BPH **Exclusion criteria** • Uncontrolled blood pressure • Hepatic or renal dysfunction • Prostate cancer • Received treatments for BPH using other alpha-blockers within 2 weeks
Interventions	**Group A:** naftopidil dose 2 **Group B:** placebo **Group C:** naftopidil dose 1
Outcomes	**Primary outcome** • IPSS change (baseline to 12 weeks (end of treatment)) **Secondary outcome** • IPSS, uroflowmetry, LUTS-GAQ (baseline to 12 weeks (end of the treatment))
Notes	**Funding sources:** Dong-A Pharmaceutical Co., Ltd. **Publication status:** NCT01922375 (final publication status has not been clarified)

BPH: benign prostatic hyperplasia; IPSS: International Prostate Symptom Score; LUTS-GAQ: Lower Urinary Tract Symptoms Global Assessment Question; PVR: postvoid residual; UTI: urinary tract infection.

DATA AND ANALYSES

Comparison 1. Naftopidil versus tamsulosin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 International Prostate Symptom Score	12	965	Mean Difference (IV, Random, 95% CI)	0.47 [-0.09, 1.04]
2 International Prostate Symptom Score-Quality of Life	11	878	Mean Difference (IV, Random, 95% CI)	0.11 [-0.09, 0.30]
3 Treatment withdrawals for any reason	8	668	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.64, 1.34]
4 Treatment withdrawals due to adverse events	9	735	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.72, 4.61]
5 Acute urinary retention	3	272	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.23, 2.86]
6 Surgical intervention	2	171	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Cardiovascular adverse events	9	824	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.52, 1.80]
8 Sexual adverse events	5	397	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.22]

Comparison 2. Naftopidil versus silodosin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 International Prostate Symptom Score	5	652	Mean Difference (IV, Random, 95% CI)	1.04 [-0.78, 2.85]
2 International Prostate Symptom Score-Quality of Life	5	652	Mean Difference (IV, Random, 95% CI)	0.21 [-0.23, 0.66]
3 Treatment withdrawals for any reason	4	659	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.23]
4 Treatment withdrawals due to adverse events	5	738	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.35, 1.51]
5 Acute urinary retention	2	180	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Surgical intervention	2	180	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Cardiovascular adverse events	5	808	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.39, 2.44]
8 Sexual adverse events	4	348	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.06, 0.42]

Comparison 3. Naftopidil versus propiverine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 International Prostate Symptom Score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 International Prostate Symptom Score-Quality of Life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 4. Naftopidil versus Eviprostat

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 International Prostate Symptom Score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 International Prostate Symptom Score-Quality of Life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Treatment withdrawals for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Treatment withdrawals due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Naftopidil versus tamsulosin, Outcome 1 International Prostate Symptom Score.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 1 International Prostate Symptom Score

Study or subgroup	Naftopidil N	Mean(SD)	Tamsulosin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fujihara 2010	39	-3.77 (5.65)	43	-3.31 (6.15)		4.5 %	-0.46 [-3.01, 2.09]
Gotoh 2005	69	-5.9 (5.82)	75	-8.4 (6.95)		6.4 %	2.50 [0.41, 4.59]
Griwan 2014	60	-9.38 (3.16)	60	-9.8 (3.65)		15.2 %	0.42 [-0.80, 1.64]
Hanyu 2010	36	-6.1 (7.2)	32	-5.3 (4.9)		3.5 %	-0.80 [-3.70, 2.10]
Ikemoto 2003	31	8.5 (6.1)	34	9.2 (5.2)		3.9 %	-0.70 [-3.47, 2.07]
Ju 2002	39	-8.82 (4.5)	38	-9.21 (4.54)		6.8 %	0.39 [-1.63, 2.41]
Kwon 2018	49	-3.8 (6.3)	45	-4 (7.1)		4.0 %	0.20 [-2.52, 2.92]
Masumori 2009	38	-3.8 (5.1)	35	-7.2 (6.1)		4.4 %	3.40 [0.81, 5.99]
Momose 2007	20	-6.7 (6.43)	25	-7.3 (7)		2.0 %	0.60 [-3.33, 4.53]
Nishino 2006	34	8.9 (3.2)	34	9.3 (3)		11.5 %	-0.40 [-1.87, 1.07]
Ukimura 2008	25	7.8 (5.1)	23	9.2 (6.6)		2.7 %	-1.40 [-4.76, 1.96]
Yokoyama 2011	42	11.3 (1.1)	39	10.7 (1.4)		35.1 %	0.60 [0.05, 1.15]
Total (95% CI)	**482**		**483**			**100.0 %**	**0.47 [-0.09, 1.04]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 13.23$, df = 11 (P = 0.28); $I^2 = 17\%$

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Naftopidil versus tamsulosin, Outcome 2 International Prostate Symptom Score-Quality of Life.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

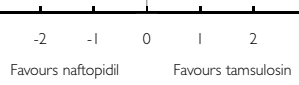
Outcome: 2 International Prostate Symptom Score-Quality of Life

Study or subgroup	Naftopidil N	Mean(SD)	Tamsulosin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fujihara 2010	39	-1.01 (1.31)	43	-0.72 (3.78)		2.3 %	-0.29 [-1.49, 0.91]
Gotoh 2005	69	-1.3 (1.66)	75	-1.4 (1.3)		9.6 %	0.10 [-0.39, 0.59]
Griwan 2014	60	-2.75 (0.56)	60	-2.75 (0.56)		19.4 %	0.0 [-0.20, 0.20]
Hanyu 2010	36	-1.8 (1.16)	32	-1.4 (1.3)		7.5 %	-0.40 [-0.99, 0.19]
Ikemoto 2003	31	3.2 (1.83)	34	3.12 (1.92)		3.8 %	0.08 [-0.83, 0.99]
Kwon 2018	49	-0.6 (1.25)	45	-0.8 (1.3)		8.9 %	0.20 [-0.32, 0.72]
Masumori 2009	38	-1 (1.2)	35	-1.9 (1.8)		5.7 %	0.90 [0.19, 1.61]
Momose 2007	20	-0.6 (0.95)	25	-0.7 (1.22)		6.8 %	0.10 [-0.53, 0.73]
Nishino 2006	34	2.6 (1.1)	34	2.7 (1.1)		8.8 %	-0.10 [-0.62, 0.42]
Ukimura 2008	16	2.5 (1.3)	22	2.8 (1.3)		4.4 %	-0.30 [-1.14, 0.54]
Yokoyama 2011	42	-1.45 (0.2)	39	-1.79 (0.3)		22.7 %	0.34 [0.23, 0.45]
Total (95% CI)	**434**		**444**			**100.0 %**	**0.11 [-0.09, 0.30]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 20.93$, df = 10 (P = 0.02); $I^2 = 52\%$

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable

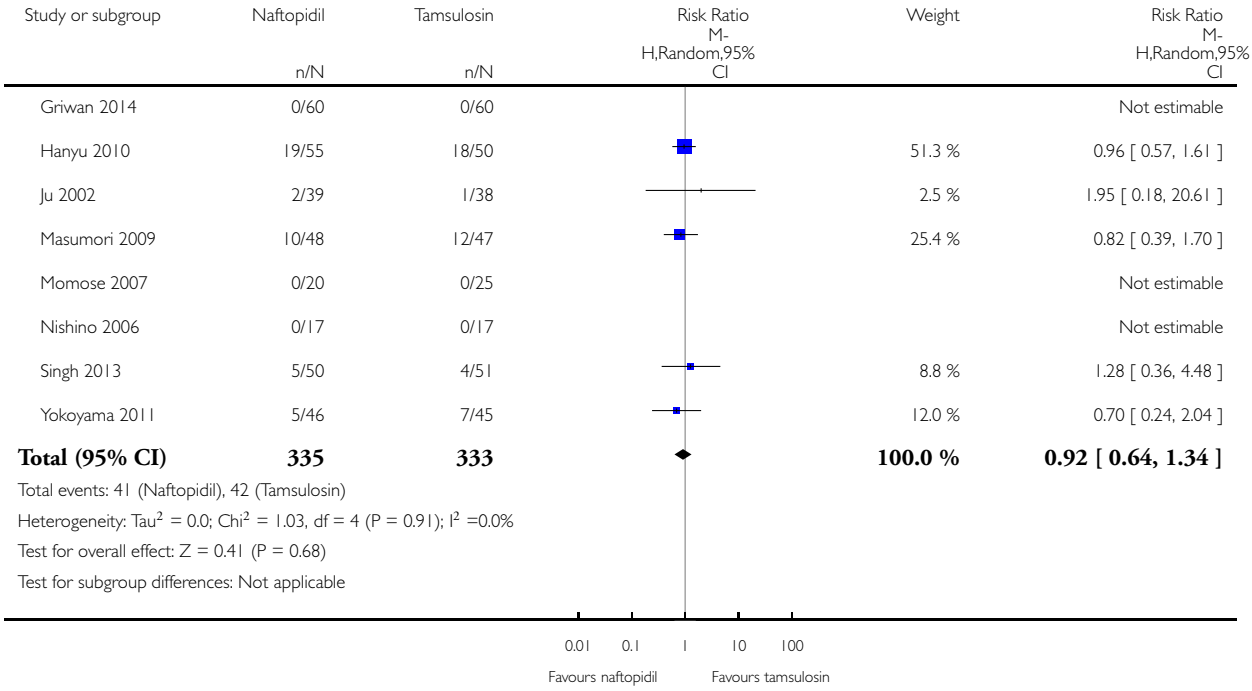


Analysis 1.3. Comparison 1 Naftopidil versus tamsulosin, Outcome 3 Treatment withdrawals for any reason.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 3 Treatment withdrawals for any reason

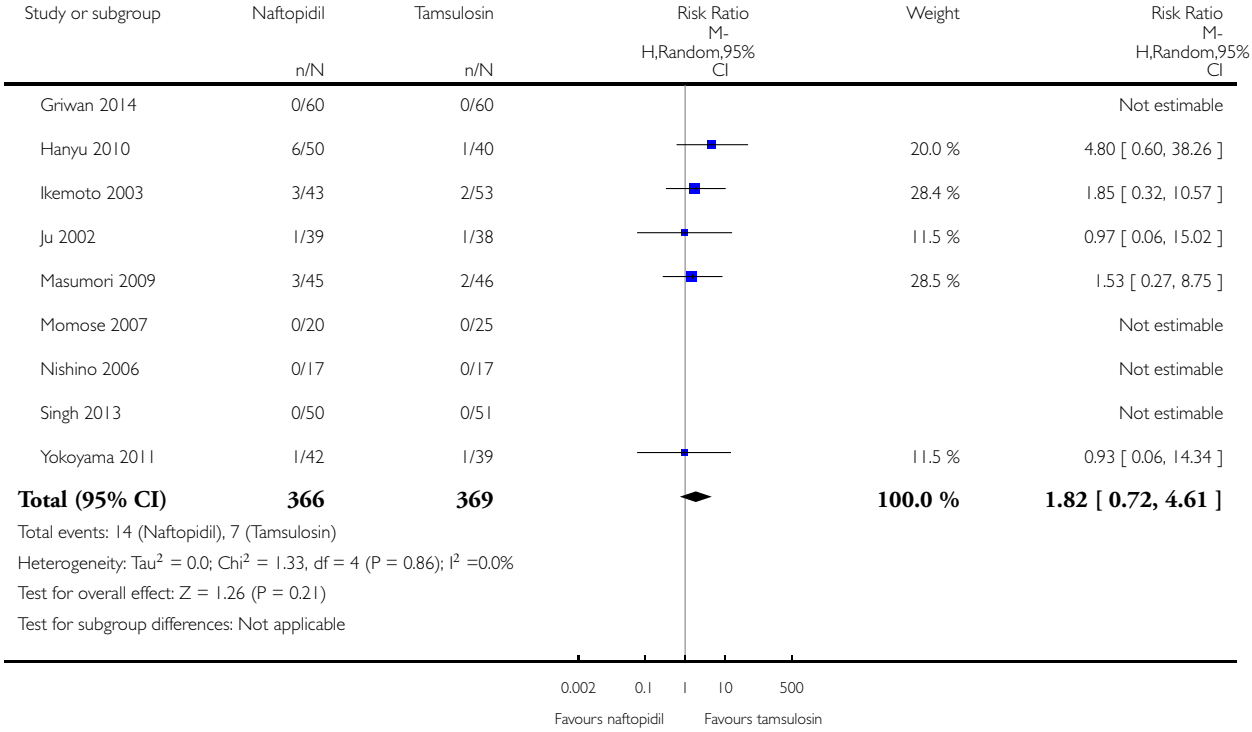


Analysis 1.4. Comparison 1 Naftopidil versus tamsulosin, Outcome 4 Treatment withdrawals due to adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 4 Treatment withdrawals due to adverse events



Analysis 1.5. Comparison 1 Naftopidil versus tamsulosin, Outcome 5 Acute urinary retention.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 5 Acute urinary retention

Study or subgroup	Naftopidil n/N	Tamsulosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hanyu 2010	0/50	0/40			Not estimable
Singh 2013	4/50	5/51		100.0 %	0.82 [0.23, 2.86]
Yokoyama 2011	0/42	0/39			Not estimable
Total (95% CI)	**142**	**130**		**100.0 %**	**0.82 [0.23, 2.86]**

Total events: 4 (Naftopidil), 5 (Tamsulosin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Naftopidil versus tamsulosin, Outcome 6 Surgical intervention.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 6 Surgical intervention

Study or subgroup	Naftopidil n/N	Tamsulosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hanyu 2010	0/50	0/40			Not estimable
Yokoyama 2011	0/42	0/39			Not estimable
Total (95% CI)	**92**	**79**			**Not estimable**

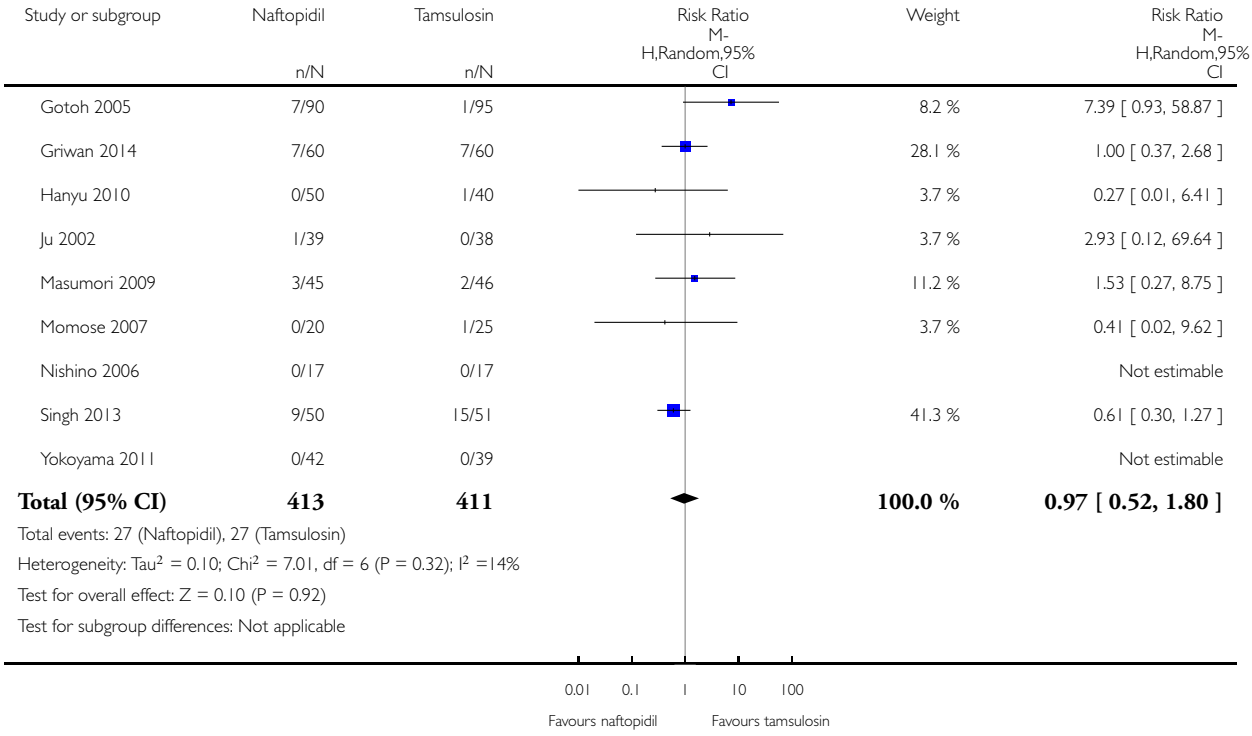
Total events: 0 (Naftopidil), 0 (Tamsulosin)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Naftopidil versus tamsulosin, Outcome 7 Cardiovascular adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 7 Cardiovascular adverse events



Analysis 1.8. Comparison 1 Naftopidil versus tamsulosin, Outcome 8 Sexual adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 1 Naftopidil versus tamsulosin

Outcome: 8 Sexual adverse events

Study or subgroup	Naftopidil n/N	Tamsulosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hanyu 2010	0/50	0/40			Not estimable
Masumori 2009	2/45	4/46		24.5 %	0.51 [0.10, 2.65]
Nishino 2006	0/17	0/17			Not estimable
Singh 2013	5/50	10/51		66.6 %	0.51 [0.19, 1.39]
Yokoyama 2011	1/42	1/39		8.9 %	0.93 [0.06, 14.34]
Total (95% CI)	**204**	**193**		**100.0 %**	**0.54 [0.24, 1.22]**

Total events: 8 (Naftopidil), 15 (Tamsulosin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.17$, df = 2 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Naftopidil versus silodosin, Outcome 1 International Prostate Symptom Score.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 1 International Prostate Symptom Score

Study or subgroup	Naftopidil N	Mean(SD)	Silodosin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Masuda 2012	34	-6.8 (4.85)	30	-8.6 (5.16)		17.3 %	1.80 [-0.66, 4.26]
Matsukawa 2017	157	-6.2 (6.55)	157	-7.5 (6.55)		21.8 %	1.30 [-0.15, 2.75]
Shirakawa 2013	56	-3.56 (5.87)	56	-6.02 (5.27)		19.1 %	2.46 [0.39, 4.53]
Yamaguchi 2013	38	-5.8 (6)	41	-7.4 (5.4)		17.0 %	1.60 [-0.92, 4.12]
Yokoyama 2011	42	-6.1 (1.1)	41	-4.9 (1.2)		24.9 %	-1.20 [-1.70, -0.70]
Total (95% CI)	**327**		**325**			**100.0 %**	**1.04 [-0.78, 2.85]**

Heterogeneity: $Tau^2 = 3.38$; $Chi^2 = 27.22$, df = 4 (P = 0.00002); $I^2 = 85\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Naftopidil versus silodosin, Outcome 2 International Prostate Symptom Score-Quality of Life.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 2 International Prostate Symptom Score-Quality of Life

Study or subgroup	Naftopidil N	Mean(SD)	Silodosin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Masuda 2012	34	-1.3 (1.24)	30	-2 (1.2)		16.9 %	0.70 [0.10, 1.30]
Matsukawa 2017	157	-1.6 (0.94)	157	-1.9 (0.94)		23.1 %	0.30 [0.09, 0.51]
Shirakawa 2013	56	-0.95 (1.27)	56	-0.98 (1.26)		19.1 %	0.03 [-0.44, 0.50]
Yamaguchi 2013	38	-1 (1.4)	41	-1.6 (1.3)		16.9 %	0.60 [0.00, 1.20]
Yokoyama 2011	42	-1.45 (0.2)	41	-1.1 (0.2)		24.1 %	-0.35 [-0.44, -0.26]
Total (95% CI)	**327**		**325**			**100.0 %**	**0.21 [-0.23, 0.66]**

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 50.20$, df = 4 ($P<0.00001$); $I^2 = 92\%$

Test for overall effect: Z = 0.93 (P = 0.35)

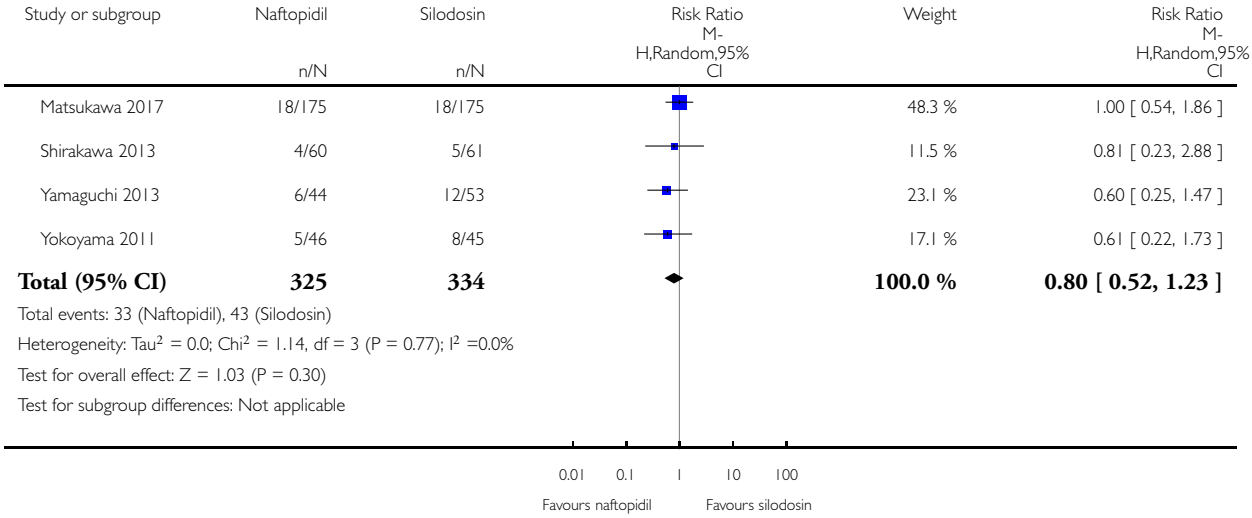
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Naftopidil versus silodosin, Outcome 3 Treatment withdrawals for any reason.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 3 Treatment withdrawals for any reason

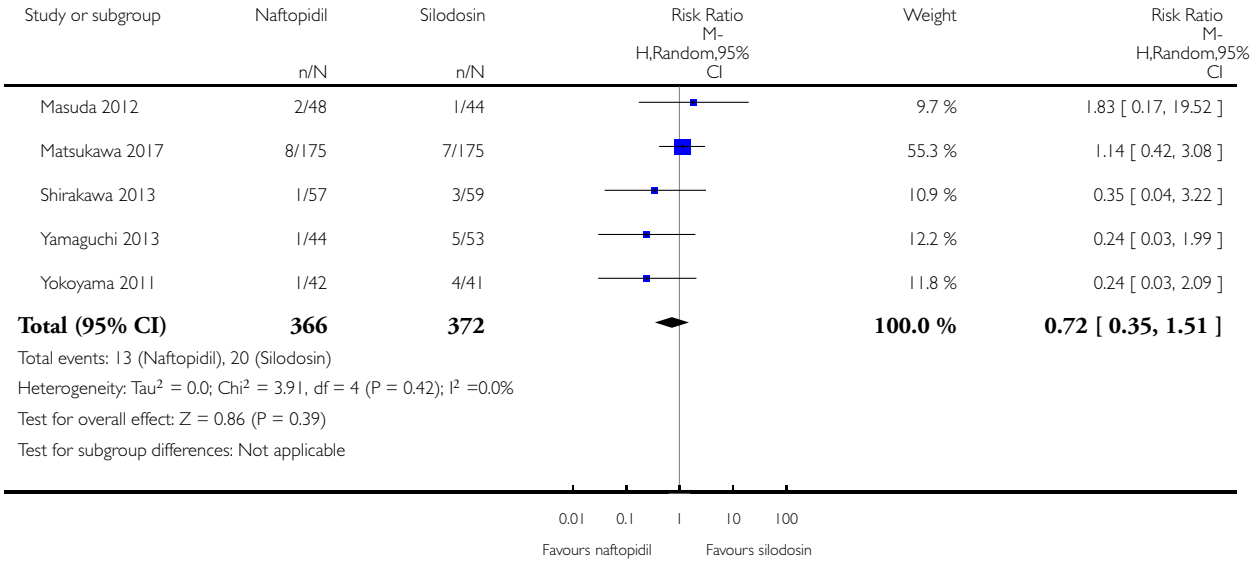


Analysis 2.4. Comparison 2 Naftopidil versus silodosin, Outcome 4 Treatment withdrawals due to adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 4 Treatment withdrawals due to adverse events



Analysis 2.5. Comparison 2 Naftopidil versus silodosin, Outcome 5 Acute urinary retention.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 5 Acute urinary retention

Study or subgroup	Naftopidil n/N	Silodosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Yamaguchi 2013	0/44	0/53			Not estimable
Yokoyama 2011	0/42	0/41			Not estimable
Total (95% CI)	**86**	**94**			**Not estimable**

Total events: 0 (Naftopidil), 0 (Silodosin)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Naftopidil versus silodosin, Outcome 6 Surgical intervention.

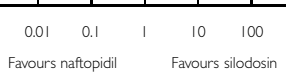
Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 6 Surgical intervention

Study or subgroup	Naftopidil n/N	Silodosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Yamaguchi 2013	0/44	0/53			Not estimable
Yokoyama 2011	0/42	0/41			Not estimable
Total (95% CI)	**86**	**94**			**Not estimable**

Total events: 0 (Naftopidil), 0 (Silodosin)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

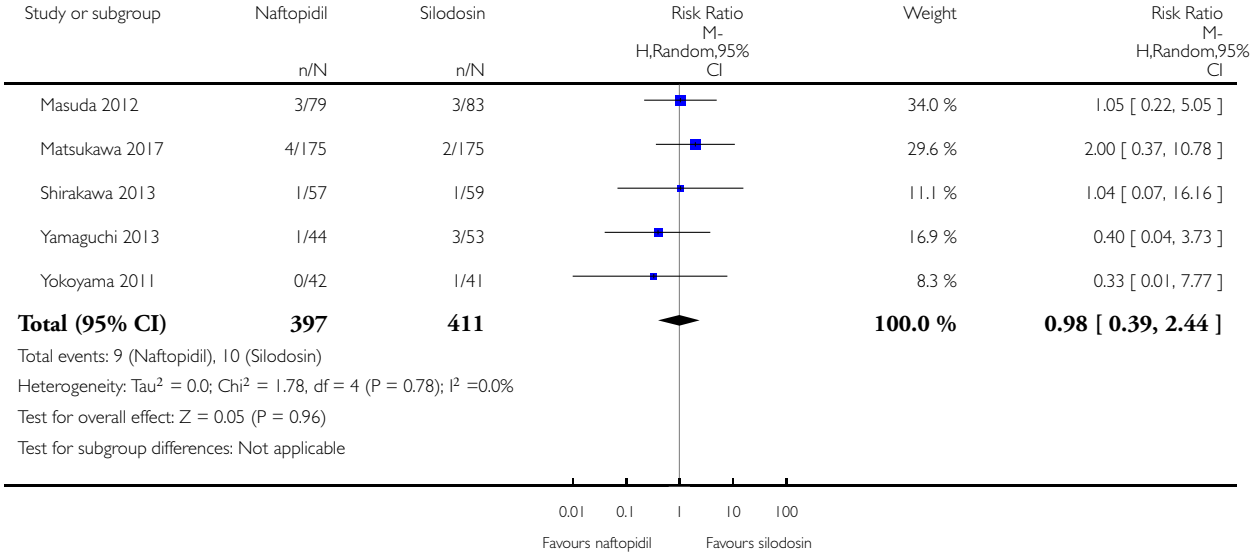


Analysis 2.7. Comparison 2 Naftopidil versus silodosin, Outcome 7 Cardiovascular adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 7 Cardiovascular adverse events



Analysis 2.8. Comparison 2 Naftopidil versus silodosin, Outcome 8 Sexual adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 2 Naftopidil versus silodosin

Outcome: 8 Sexual adverse events

Study or subgroup	Naftopidil n/N	Silodosin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Masuda 2012	0/79	5/83		12.0 %	0.10 [0.01, 1.70]
Shirakawa 2013	0/57	1/59		9.8 %	0.34 [0.01, 8.29]
Yamaguchi 2013	2/21	10/23		50.8 %	0.22 [0.05, 0.89]
Yokoyama 2011	1/15	10/11		27.4 %	0.07 [0.01, 0.49]
Total (95% CI)	**172**	**176**		**100.0 %**	**0.15 [0.06, 0.42]**

Total events: 3 (Naftopidil), 26 (Silodosin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.21$, df = 3 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 3.69 (P = 0.00023)

Test for subgroup differences: Not applicable

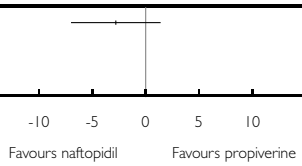
Analysis 3.1. Comparison 3 Naftopidil versus propiverine, Outcome 1 International Prostate Symptom Score.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 3 Naftopidil versus propiverine

Outcome: 1 International Prostate Symptom Score

Study or subgroup	Naftopidil N	Mean(SD)	Propiverine N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yokoyama 2009	19	-4.9 (5.85)	18	-2.1 (7.05)		-2.80 [-6.99, 1.39]



Analysis 3.2. Comparison 3 Naftopidil versus propiverine, Outcome 2 International Prostate Symptom Score-Quality of Life.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 3 Naftopidil versus propiverine

Outcome: 2 International Prostate Symptom Score-Quality of Life

Study or subgroup	Naftopidil N	Mean(SD)	Propiverine N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yokoyama 2009	19	-0.9 (1.02)	18	-1 (1.02)		0.10 [-0.56, 0.76]

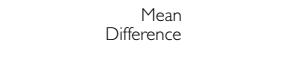
Analysis 4.1. Comparison 4 Naftopidil versus Eviprostat, Outcome 1 International Prostate Symptom Score.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 4 Naftopidil versus Eviprostat

Outcome: 1 International Prostate Symptom Score

Study or subgroup	Naftopidil N	Mean(SD)	Eviprostat N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yamanishi 2004	36	-5.9 (4.3)	13	0.4 (5.2)		-6.30 [-9.46, -3.14]



Analysis 4.2. Comparison 4 Naftopidil versus Eviprostat, Outcome 2 International Prostate Symptom Score-Quality of Life.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 4 Naftopidil versus Eviprostat

Outcome: 2 International Prostate Symptom Score-Quality of Life

Study or subgroup	Naftopidil N	Mean(SD)	Eviprostat N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yamanishi 2004	36	-1.5 (1.5)	13	0 (1.3)		-1.50 [-2.36, -0.64]

Analysis 4.3. Comparison 4 Naftopidil versus Eviprostat, Outcome 3 Treatment withdrawals for any reason.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 4 Naftopidil versus Eviprostat

Outcome: 3 Treatment withdrawals for any reason

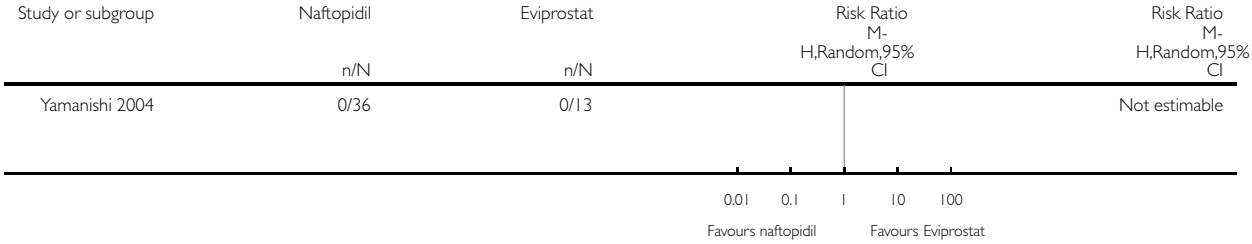
Study or subgroup	Naftopidil n/N	Eviprostat n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Yamanishi 2004	0/36	0/13		Not estimable

Analysis 4.4. Comparison 4 Naftopidil versus Eviprostat, Outcome 4 Treatment withdrawals due to adverse events.

Review: Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia

Comparison: 4 Naftopidil versus Eviprostat

Outcome: 4 Treatment withdrawals due to adverse events



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)	Mean age (± SD; years)	Mean prostate volume (± SD; mL)	IPSS (± SD)
Fujihara 2010	NR	Japan	Multicentre	Men with LUTS with OAB symptoms	Naftopidil 50-75 mg once daily	12 weeks	NR	NR	17.61 ± 5.8 (estimated from the figure)
					Tamsulosin 0.2 mg once daily		NR	NR	15.72 ± 6.96 (estimated from the figure)
Gotoh 2005	NR	Japan	Multicentre (16 investigational sites)	Men aged ≥ 50 years, IPSS ≥ 8, Q_{max} < 15 mL/s (voided volume ≥	Naftopidil 25 mg/day for 2 weeks, followed by 50 mg/day for 10	12 weeks	68.0 ± 7.2 (calculated from 95% CI 66.4 to 69.8)	29.0 ± 10.2 (calculated from 95% CI 27.2 to 32.0)	15.5 ± 5.7 (calculated from 95% CI 14.1 to 16.8)

Table 1. Baseline characteristics of included studies (*Continued*)

				150 mL), prostate ≥ 20 mL	weeks				
					Tamsulosin 0.2 mg/day for 12 weeks		68.5 ± 6.8 (calculated from 95% CI 67.0 to 70.1)	33.6 ± 18.1 (calculated from 95% CI 29.5 to 37.7)	17.1 ± 6.18 (calculated from 95% CI 15.7 to 18.5)
Griwan 2014	NR	India	Single institution	Men aged ≥ 45 years, daytime frequency > 8, nocturnal frequency > 2, Q_{max} 5-15 mL/s (150 mL voided volume), PVR < 150 mL, IPSS > 13, IPSS bother score > 3	Naftopidil 75 mg/day	3 months	NR	56.81 ± 6.45	21.31 ± 4.04
					Tamsulosin 0.4 mg/day		NR	57.73 ± 7.33	21.95 ± 4.46
Hanyu 2010	2005-2008	Japan	Multicentre (4 centres)	Men aged ≥ 50 years at first visit, total IPSS ≥ 8, QoL index score ≥ 2 prostate volume ≥ 20 mL, PVR < 100 mL	Naftopidil 50 mg/day	12 weeks	70.5 ± 5.8	40.2 ± 16.3	14.8 ± 5.7
					Tamsulosin 0.2 mg/day		70.9 ± 5.8	41.0 ± 19.3	13.5 ± 5.0
Ikemoto 2003	2000-2002	Japan	3 hospitals in single institute	IPSS ≥ 8; Q_{max} < 12 mL/s (150 mL voiding); if prior BPH medication, 1 month	Naftopidil 25 mg/day for first 2 weeks, then 50 mg once daily for 6 weeks then tamsulosin 0.2	8 weeks (additional 8 weeks after cross-over/ no washout)	66.6 ± 7.6	38.9 ± 11.8	17.4 ± 6.0

Table 1. Baseline characteristics of included studies (*Continued*)

				washout period	mg for 8 weeks				
					Tamsulosin 0.2 mg for 8 weeks then naftopidil 25 mg for 2 weeks, then 50 mg for 6 weeks		63.8 ± 9.1	32.7 ± 9.4	16.8 ± 7.2
Ju 2002	2011	China	Single institution	Men aged 50-75 years with BPH, IPSS ≥ 13, PSA ≤ 4 ng/mL, Q_{max} 5-15 mL/s when urine volume > 150 mL	Naftopidil 25 mg once daily	6 weeks	62.5 ± 5.26	NR	18.79 ± 4.8
					Tamsulosin 0.2 mg once daily		66.5 ± 5.8	NR	19.71 ± 4.7
Kwon 2018	2015	Korea	Multicentre	94 men who had been taking tamsulosin for more than 8 weeks; however, men who persisted > 3 points of OABSS, especially > 2 points of OABSS question 3	Naftopidil 75 mg/day for 8 weeks	8 weeks	66.0 ± 6.3	36.8 ± 14.6	16.9 ± 6.2
					Tamsulosin 0.2 mg once daily for 8 weeks		64.8 ± 7.7	37.5 ± 22.4	19.1 ± 7.2
Li 2007	2002-2003	China	Multicentre (9 centres)	Men with BPH/LUTS aged 50-75 years, total IPSS ≥ 13, prostate	Naftopidil 25 mg once daily	12 month	67.7 ± 5.5	38.1 ± 15.4	20.6 ± 5.4

Table 1. Baseline characteristics of included studies (*Continued*)

				volume > 20 mL, Q_{max} < 15 mL/s, PVR < 60 mL	Tamsulosin 0.2 mg once daily		66.8 ± 5.4	43.1 ± 17.7	21.1 ± 5.6
Masuda 2012	2009-2011	Japan	Multicentre	Men with LUTS/BPH, prostate volume ≥ 20 cm^3, IPSS ≥ 8, QoL score ≥ 3, clinical diagnosis of BPH, aged ≥ 50 years, no prior treatment for BPH	Naftopidil 50-75 mg once/daily for 2 weeks, then 75 mg once daily for 4 weeks	6 weeks (additional 6 weeks after cross-over, no washout)	68.5 ± 5.7	45.7 ± 17.8	17.6 ± 5.0
					Silodosin 2-4 mg twice daily for 2 weeks, then 4 mg twice daily for 4 weeks		66.5 ± 5.6	38.8 ± 13.1	18.6 ± 5.5
Masumori 2009	2005-2006	Japan	Multicentre (17 centres)	Men with LUTS/BPH, aged 51-79 years, IPSS ≥ 8	Naftopidil 50 mg once daily	12 weeks	64.5 ± 7.7	35.9 ± 15.3	15.0 ± 5.9
					Tamsulosin 0.2 mg once daily		65.2 ± 7.5	34.4 ± 13.7	17.8 ± 5.7
Matsukawa 2017	2012-2013	Japan	Multicentre	Men aged ≥ 50 years, total IPSS ≥ 8, IPSS-QoL score ≥ 3, total OABSS ≥ 3, ≥ 1 urinary urgency episodes/	Naftopidil 50 mg/day for 4 weeks, followed by 75 mg/day for 8 weeks	12 weeks	70.3 ± 7.8	38.6 ± 14.8	18.9 ± 6.1

Table 1. Baseline characteristics of included studies (*Continued*)

				week, prostate volume ≥ 20 mL on transabdominal ultrasonography, Q_{max} < 15 mL/s at a voided volume of ≥ 100 mL and PVR < 150 mL	Silodosin 4 mg/day for 4 weeks, followed by 8 mg/day for 8 weeks		70.6 ± 7.8	39.6 ± 16.7	18.8 ± 6.2
Momose 2007	2002-2003	Japan	Single centre	Men with LUTS with BPH	Naftopidil 50 mg/day for 4 weeks then tamsulosin 0.2 mg/day for 4 weeks	28 days (additional 28 days after cross-over, no washout)	65.3 ± 5.5	30.7 ± 13.8	19.6 ± 7.0
					Tamsulosin 0.2 mg/day for 4 weeks and naftopidil 50 mg/day 4 weeks		68.2 ± 7.7	47.2 ± 22.6	18.4 ± 6.9
Nishino 2006	NR	Japan	Single centre	Men with LUTS secondary to BPH	Naftopidil 50 mg/day for 4 weeks then tamsulosin 0.2 mg for 4 weeks	4 weeks: data analysis (4 weeks before cross-over. 1-week washout, and additional 4 weeks after cross-over)	73.2 ± 4.1	20.6 ± 3.7	20.7 ± 4.3
					Tamsulosin		71.5 ± 4.5	18.9 ± 2.8	20.1 ± 2.7

Table 1. Baseline characteristics of included studies (*Continued*)

					0.2 mg/day for 4 weeks then naftopidil 50 mg for 4 weeks				
Perumal 2015	2011-2013	India	Single centre	Men aged > 50 years, clinical symptoms of BPE, LUTS, with or without raised PVR urine	Naftopidil 50 mg once daily	30 days	59.9 ± 5.5	NR	19.97 ± 2.53
					Tamsulosin 0.4 mg once daily		60.1 ± 5.0	NR	21.3 ± 2.84
Shirakawa 2013	2007-2011	Japan	Kobe University School or other collaborating institutions	Men with BPH/LUTS, total IPSS 8 points, QoL index 3 points, Q_{max} < 15 mL/s, prostate volume 20 mL; either men without history of using any a1-receptor blocker (hereafter, drug-naive group) or men who had continued to use tamsulosin 0.2 mg once daily for ≥ 3	Naftopidil 50 mg once daily	8 consecutive weeks	70.50 ± 6.58	39.39 ± 25.96	17.56 ± 6.73

Table 1. Baseline characteristics of included studies (*Continued*)

				months and wanted to switch the medication to another oral drug (hereafter, drug-switching group)	Silodosin 4 mg twice daily		70.98 ± 6.69	38.24 ± 12.94	17.53 ± 5.4
Singh 2013	2010-2012	India	Single institution	Men with BPH; IPSS > 8 or > 3 points for frequency, nocturia, and urgency on IPSS; prostate volume > 15 mL, or peak flow rate < 10 mL for voided volume > 150 mL	Naftopidil 50 mg once daily	12 weeks	61.69	31.38	21.06
					Tamsulosin 0.4 mg once daily		61.15	30.01	21.53
Ub 2016	2009-2013	Japan	Multicentre	Men with OAB and BPH, who met the following criteria and were not administered medication (except herbal preparation) for urinary disorder: IPSS ≥ 2, QoL	Naftopidil 75 mg/day	8 weeks (additional 8 weeks after cross-over, no washout: authors judged that evaluation without washout period would be feasible)	74.7 ± 8.0	NR	17.4 ± 6.7

Table 1. Baseline characteristics of included studies (*Continued*)

				score ≥ 2, OABSS ≥ 3 (urgency score ≥ 2)	Tamsulosin 0.2 mg/day + solifenacin 5 mg/day		71.9 ± 8.3	NR	18.1 ± 5.4
Ukimura 2008	2004-2007	Japan	Multicentre	Men aged ≥ 50 years, number of nocturia ≥ 2, IPSS ≥ 8, QoL index ≥ 3, residual urine volume < 50 mL (evaluated by ultrasound estimation), maximum voiding flow rate < 15 mL/s (preferably with a urination volume ≥ 150 mL), prostate volume < 50 mL	Naftopidil 50 mg once daily	6-8 weeks	69.6 ± 6.8	24.4 ± 6.9	17.2 ± 6.4
					Tamsulosin 0.2 mg once daily		68.8 ± 8.2	26.7 ± 7.9	18.9 ± 6.6
Yamaguchi 2013	2007-2010	Japan	Multicentre	Men with BPH aged ≥ 50 years, significant LUTS and deteriorated QoL, IPSS ≥ 8, IPSS-QoL score	Naftopidil 75 mg/day	12 weeks	70.0 ± 7.0	39.5 ± 18.0	18.9 ± 7.0

Table 1. Baseline characteristics of included studies (*Continued*)

				≥ 3					
					Silodosin 8 mg/day		69.3 ± 7.8	33.2 ± 21.2	16.9 ± 5.5
Yamanishi 2004	NR	Japan	Single centre	IPSS ≥ 8, Q_{max} < 12 mL/s, prostate volume ≥ 15 mL, obstructive (or equivocal) condition on International Continence Society nomogram as assessed in a pressure/flow study	Naftopidil 25 mg once daily for 2 weeks, then 50 mg once daily for 2 weeks, then 75 mg once daily for 2 weeks	6 weeks	67.5 ± 8.2	29.7 ± 14.9	15.4 ± 5.7
					Eviprostat 6 tablets daily		69.0 ± 6.5	29.5 ± 15.9	16.0 ± 6.9
Yokoyama 2009	2004-2007	Japan	2 centres	Men aged ≥ 50 years, IPSS ≥ 8, 2-day frequency volume chart showing ≥ 1 episode/day of urinary urgency, daytime voiding frequency ≥ 8 episodes/day, nighttime voiding frequency ≥ 1 episode/night, PVR	Naftopidil 50 mg/day	4 weeks	69.1 ± 8.3	26.6 ± 12.3	18.2 ± 5.7

Table 1. Baseline characteristics of included studies (*Continued*)

				≤ 50 mL. Men with elevated serum PSA level (> 10 ng/mL) were confirmed as having BPH before the treatment by transrectal ultrasound-guided prostate sextant biopsies					
					Propiverine hydrochloride 20 mg/day		70.9 ± 6.7	25.3 ± 7.7	18.2 ± 7.0
Yokoyama 2011	NR	Japan	2 centres	Men with LUTS aged 50-80 years, IPSS ≥ 8	Naftopidil 50 mg once daily	12 weeks	69.1 ± 1.2	35.0 ± 3.1	17.4 ± 0.8
					Tamsulosin 0.2 mg once daily		71.5 ± 1.1	32.5 ± 2.0	18.0 ± 1.1
					Silodosin 4 mg twice daily		70.2 ± 0.9	33.3 ± 2.3	18.7 ± 0.7

BPE: benign prostatic enlargement; BPH: benign prostatic hyperplasia; CI: confidence interval; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; NR: not reported; OAB: overactive bladder; OABSS: overactive bladder symptom score; PSA: prostate-specific antigen; PVR: postvoid residual; Q_{max}: maximum flow rate; QoL: quality of life; s: second; SD: standard deviation.

Table 2. Participants in included studies

Study name	Intervention(s) and comparator(s)	Screened/eligible (n)	Randomised (n)	Analysed (n)	Finishing trial (n (%))
Fujihara 2010	Naftopidil 50-75 mg once daily	NR/82	39	NR	NR

Table 2. Participants in included studies (*Continued*)

	Tamsulosin 0.2 mg once daily		43	NR	NR
	Total		82	NR	NR
Gotoh 2005	Naftopidil 25 mg/day for 2 weeks, followed by 50 mg/day for 10 weeks	185/144	69	69	69
	Tamsulosin 0.2 mg/day		75	75	75
	Total		144	144	144 (100)
Griwan 2014	Naftopidil 75 mg/day	NR/120	60	60	60
	Tamsulosin 0.4 mg/day		60	60	60
	Total		120	120	120 (100)
Hanyu 2010	Naftopidil 50 mg/day	NR/105	55	36	36
	Tamsulosin 0.2 mg/day		50	32	32
	Total		105	68	68 (64.8)
Ikemoto 2003	Naftopidil 25 mg/day for first 2 weeks, then 50 mg once daily for 6 weeks then tamsulosin 0.2 mg for 8 weeks	NR/96	43	31	31
	Tamsulosin 0.2 mg for 8 weeks then naftopidil 25 mg for 2 weeks, then 50 mg for 6 weeks		53	34	34
	Total		96	65	65 (67.7)
Ju 2002	Naftopidil 25 mg once daily	80/80	40	39	39

Table 2. Participants in included studies (*Continued*)

	Tamsulosin 0.2 mg once daily		40	38	38
	Total		80	77	77 (96.3)
Kwon 2018	Naftopidil 75 mg/day	NR/94	49	NR	NR
	Tamsulosin 0.2 mg once daily		45	NR	NR
	Total		94	-	-
Li 2007	Naftopidil 25 mg once daily	906/906	126	NR	NR
	Tamsulosin 0.2 mg once daily		138	NR	NR
	Total		264	-	-
Masuda 2012	Naftopidil 50-75 mg once for 2 weeks, then 75 mg once daily for 4 weeks	NR/92	48	34	34
	Silodosin 2-4 mg twice daily for 2 weeks, then 4 mg twice daily for 4 weeks		44	30	30
	Total		92	64	64 (69.6)
Masumori 2009	Naftopidil 50 mg/day	NR/95	48	38	38
	Tamsulosin 0.2 mg/day		47	35	35
	Total		95	73	73 (76.8)
Matsukawa 2017	Naftopidil 50 mg for 4 weeks, then 75 mg for 8 weeks	NR/350	175	157	157
	Silodosin 4 mg for 4 weeks, then 8 mg for 8 weeks		175	157	157

Table 2. Participants in included studies (*Continued*)

	Total		350	314	314 (89.7)
Momose 2007	Naftopidil 50 mg/ 4 weeks, then tamsulosin 0.2 mg/day for 4 weeks	NR/45	20	20	20
	Tamsulosin 0.2 mg for 4 weeks, then naftopidil 50 mg/ day for 4 weeks		25	25	25
	Total		45	45	45 (100)
Nishino 2006	Naftopidil 50 mg/ day 4 weeks, then tamsulosin 0.2 mg/ day 4 weeks	NR/34	17	17	17
	Tamsulosin 0.2 mg/ day 4 weeks, then naftopidil 50 mg/ day 4 weeks		17	17	17
	Total		34	34	34 (100)
Perumal 2015	Naftopidil 50 mg once daily	NR/60	30	NR	NR
	Tamsulosin 0.4 mg once daily		30	NR	NR
	Total		60	NR	NR
Shirakawa 2013	Naftopidil 50 mg once daily	NR/121	60	56/57	56
	Silodosin 4 mg twice daily		61	56/59	56
	Total		121	112/116	112 (92.5)
Singh 2013	Naftopidil 50 mg once daily	NR/110	55	50	50
	Tamsulosin 0.4 mg once daily		55	51	51

Table 2. Participants in included studies (*Continued*)

	Total		110	101	101 (91.8)
Ub 2016	Naftopidil 75 mg/day	NR/59	NR	14	14
	Tamsulosin 0.2 mg/day + solifenacin 5 mg/day		NR	17	17
	Total		NR	31	31
Ukimura 2008	Naftopidil 50 mg once daily	NR/81	NR	31	31
	Tamsulosin 0.2 mg once daily		NR	28	28
	Total		NR	59	59
Yamaguchi 2013	Naftopidil 75 mg/day	109/109	51	44	44
	Silodosin 8 mg/day		58	53	53
	Total		109	97	97 (90.0)
Yamanishi 2004	Naftopidil 25 mg once daily for 2 weeks, then 50 mg once daily for 2 weeks, and then 75 mg once daily for 2 weeks	NR/49	36	36	36
	Eviprostat 6 tablets daily		13	13	13
	Total		49	49	49 (100)
Yokoyama 2009	Naftopidil 50 mg/day	NR/58	19	19	19
	Propiverine hydrochloride 20 mg/day		18	18	18
	Total		37	37	37 (100)

Table 2. Participants in included studies (*Continued*)

Yokoyama 2011	Naftopidil 50 mg once daily	136/136	46	42	42
	Tamsulosin 0.2 mg once daily		45	39	39
	Silodosin 4 mg twice daily		45	41	41
	Total		136	122	122 (89.7)
Overall total	Interventions: naftopidil	Ub 2016; Ukimura 2008 did not report	1086[a]	-	793[b]
	Comparator: tamsulosin	Ub 2016; Ukimura 2008 did not report	723[a]	-	451[b]
	Comparator: silodosin	-	383	-	337 (87.9)
	Comparator: propiverine	-	18	-	18 (100)
	Comparator: Eviprostat	-	13	-	13 (100)
	Overall	-	2223	-	1612 (72.5)

n: number; NR: not reported.

[a]Two included studies did not report the number of randomised participants (Ub 2016; Ukimura 2008).

[b]Four included studies did not report the number of participants who finished trials (Fujihara 2010; Kwon 2018; Li 2007; Perumal 2015).

APPENDICES

Appendix 1. Search strategies

The Cochrane Library (via Wiley) search strategy	
1	'MeSH descriptor: [Prostatic Hyperplasia] explode all trees
2	(prostat* near/3 hyperplasia*):ti,ab,kw (Word variations have been searched)
3	(prostat* near/3 hypertroph*):ti,ab,kw (Word variations have been searched)
4	(prostat* near/3 adenoma*):ti,ab,kw (Word variations have been searched)
5	(BPH or BPO or BPE):ti,ab,kw (Word variations have been searched)
6	(prostat* near/3 (enlarg* or obstruct*)):ti,ab,kw (Word variations have been searched)
7	MeSH descriptor: [Prostatism] explode all trees
8	prostatism:ti,ab,kw (Word variations have been searched)
9	MeSH descriptor: [Urinary Bladder Neck Obstruction] explode all trees
10	((bladder* near/3 obstruct*) or BOO):ti,ab,kw (Word variations have been searched)
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	'(Naftopidil or BM-15275 or KT-611 or R9PHW59SFN):ti,ab,kw (Word variations have been searched)
13	#11 and #12
MEDLINE (via PubMed) search strategy	
1	exp Prostatic Hyperplasia/
2	(Prostat* adj3 hyperplasia*).tw.
3	(Prostat* adj3 hypertroph*).tw.
4	(Prostat* adj3 adenoma*).tw.
5	(BPH or BPO or BPE).tw.
6	(prostat* adj3 (enlarg* or obstruct*)).tw.

(*Continued*)

7	exp Prostatism/
8	Prostatism.tw.
9	exp Urinary Bladder Neck Obstruction/
10	(Bladder* adj3 obstruct*).tw.
11	BOO.tw.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	'(Naftopidil or BM-15275 or KT-611 or R9PHW59SFN).nm,tw.
14	'(Flivas or Nafodil or Naftomax or Dishuang or Ge Rui Jia or Jun Lie Xin or Kun Da or Lai Luo Er or Na Tuo or Pu Chang or Shu Er or Sitandi or Yu Chang or Zai Chang).nm,tw
15	'57149-07-2.rn.
16	13 or 14 or 15
17	12 and 15
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.
20	randomized.ab.
21	placebo.ab.
22	drug therapy.fs.
23	randomly.ab.
24	trial.ab.
25	groups.ab.
26	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
27	exp animals/ not humans.sh.
28	27 not 28
29	18 and 29

(*Continued*)

Embase (via Elsevier) search strategy	
1	”prostate hypertrophy’/exp
2	(Prostat* NEAR/3 hyperplasia*):ab,ti
3	(Prostat* NEAR/3 hypertroph*):ab,ti
4	(Prostat* NEAR/3 adenoma*):ab,ti
5	”bph’:ab,ti OR ’bpo’:ab,ti OR ’bpe’:ab,ti
6	(prostat* NEAR/3 (enlarg* or obstruct*)):ab,ti
7	”prostatism’/exp
8	”prostatism’:ab,ti
9	”bladder obstruction’/exp
10	(bladder* NEAR/3 obstruct*):ab,ti
11	”BOO’:ab,ti
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	”naftopidil’/exp
14	’(Naftopidil or BM-15275 or KT-611 or R9PHW59SFN):ab,ti,tn
15	’(Flivas or Nafodil or Naftomax or Dishuang or ’Ge Rui Jia’ or ’Jun Lie Xin’ or ’Kun Da’ or ’Lai Luo Er’ or ’Na Tuo’ or ’Pu Chang’ or ’Shu Er’ or ’Sitandi’ or ’Yu Chang’ or ’Zai Chang’):ab,ti,tn
16	”57149-07-2’:rn
17	#13 OR #14 OR #15 OR #16
18	#12 AND #17
19	”crossover procedure’:de OR ’double-blind procedure’:de OR ’randomized controlled trial’:de OR ’single-blind procedure’:de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti

(*Continued*)

20	'animals'/exp NOT ('humans'/exp AND 'animals'/exp)
21	#19 NOT #20
22	#18 AND #21
Scopus search strategy	
1	TITLE-ABS-KEY((hyperplasia* W/3 prostat*) OR (hypertroph* W/3 prostat*) OR (adenoma* W/3 prostat*) OR (prostat* W/3 (enlarg* OR obstruct*)) OR (bph OR bpo OR bpe OR boo) OR prostatism OR (bladder* W/3 obstruct*))
2	TITLE-ABS-KEY(Naftopidil or BM-15275 or KT-611 or R9PHW59SFN or Flivas or Nafodil or Naftomax or Dishuang or "Ge Rui Jia" or "Jun Lie Xin" or "Kun Da" or "Lai Luo Er" or "Na Tuo" or "Pu Chang" or "Shu Er" or "Sitandi" or "Yu Chang" or "Zai Chang")
3	CASREGNUMBER (57149-07-2)
4	CHEMNAME (naftopidil OR bm-15275 OR kt-611 OR r9phw59sfn OR flivas OR nafodil OR naftomax OR dishuang OR "Ge Rui Jia" OR "Jun Lie Xin" OR "Kun Da" OR "Lai Luo Er" OR "Na Tuo" OR "Pu Chang" OR "Shu Er" OR "Sitandi" OR "Yu Chang" OR "Zai Chang")
5	#2 OR #3 OR #4
6	#1 AND #5
Web of Science search strategy	
1	TS= ((hyperplasia* NEAR/3 prostat*) OR (hypertroph* NEAR/3 prostat*) OR (adenoma* NEAR/3 prostat*) OR (prostat* NEAR/3 (enlarg* OR obstruct*)) OR (bph OR bpo OR bpe OR boo) OR prostatism OR (bladder* NEAR/3 obstruct*))
2	TS= (Naftopidil or BM-15275 or KT-611 or R9PHW59SFN or Flivas or Nafodil or Naftomax or Dishuang or "Ge Rui Jia" or "Jun Lie Xin" or "Kun Da" or "Lai Luo Er" or "Na Tuo" or "Pu Chang" or "Shu Er" or "Sitandi" or "Yu Chang" or "Zai Chang")
3	1 AND 2
LILAC search strategy	
1	(mh:("Prostatic Hyperplasia" OR prostatism OR "Urinary Bladder Neck Obstruction")) OR (tw:("Prostatic Hyperplasia" OR "Prostatic Adenoma" OR "Prostatic Hypertrophy" OR "Prostatic Enlargement" OR bph OR bpo OR bpe OR prostatism OR "Bladder Neck Obstruction" OR "Bladder Outlet Obstruction"

(*Continued*)

	OR boo)) AND (tw:(naftopidil OR bm-15275 OR kt-611 OR r9phw59sfn OR flivas OR nafodil OR naftomax OR dishuang OR "Ge Rui Jia" OR "Jun Lie Xin" OR "Kun Da" OR "Lai Luo Er" OR "Na Tuo" OR "Pu Chang" OR "Shu Er" OR "Sitandi" OR "Yu Chang" OR "Zai Chang")) AND (instance:"regional")
World Health Organization International Clinical Trials Registry Platform Search Portal	
1	prostat* AND naftopidil
ClinicalTrials.gov	
1	Prostate
2	Naftopidil
3	1 AND 2
Grey literature (Open Grey)	
1	prostat* AND naftopidil

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

Study	Date trial author contacted (first)	Date trial author provided data (latest)	Data trial author provided (short summary)
Kwon 2018	23 October 2017	23 October 2017	All data provided
Yamaguchi 1992	29 May 2018	4 June 2018	We requested full data set; however, we received author's reply as follows; "I have no way to access information on these old studies."
Yamaguchi 1997	29 May 2018	4 June 2018	We requested full data set; however, we received author's reply as follows; "I have no way to access information on these old studies."
Yamaguchi 2013	17 January 2017	30 January 2017	All data provided
Yokoyama 2011	30 January 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 end-

(*Continued*)

			point (12 weeks), the number of participants with acute urinary retention, and surgical intervention. Method of random sequence generation and blinding

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

WHAT'S NEW

Last assessed as up-to-date: 15 June 2009.

Date	Event	Description
19 April 2018	New citation required and conclusions have changed	In this update we added 16 new studies and excluded 2 studies included in the previous review due to a wrong comparator. We applied current MECIR standards as well as GRADE to assess the certainty of evidence. The conclusions of this review have changed
17 January 2012	Amended	Added grant 5R01DK63300-4 info.

CONTRIBUTIONS OF AUTHORS

ECH: study selection, extracting data, performing data analysis, interpretation of data, and drafting the review.

SG: extracting data and assessing risk of bias.

JHJ: conception and study design, searching for trials, study selection, extracting data, assessing risk of bias, performing data analysis, and interpretation of data.

MI: providing clinical and methodological advice on the review.

MHK: creating search strategies and searching for trials.

RP: providing clinical and methodological advices on the review.

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

DECLARATIONS OF INTEREST

ECH: none known.

SG: none known.

JHJ: none known.

MI: none known.

MHK: none known.

RP: none known.

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.

SOURCES OF SUPPORT

Internal sources

- Chonnam National University Medical School, Gwangju, Korea, South.
- Minneapolis VA Medical Center, Minneapolis, Minnesota, USA.
- University of Minnesota, Minneapolis, Minnesota, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol and was an update of a Cochrane Review first published in 2009 (Garimella 2009). Major differences between the previous review and the update include the following.

- A more comprehensive search performed using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, LILAC, 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.
- Types of interventions: we reclassified the types of intervention according to the drug class.
- Types of outcome measures: we renamed primary and secondary outcomes and added details in 'Method and timing of outcome measurement' for all outcomes.
- We applied the GRADE approach and the Cochrane 'Risk of bias' assessment tool to assess the certainty of evidence.
- We added new type of alpha-blocker (silodosin) as a comparator.
- We did not perform subgroup analyses based on naftopidil dose.
- We included studies using a tamsulosin dose of 0.4 mg as a comparator.
- Although the relevant outcomes could not be used in analyses, we identified one trial comparing naftopidil to placebo.

NOTES

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

Large parts of the background section of this review were based on that of a published review on silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Jung 2017). This was done with explicit approval of both the authors of this published review and the Cochrane Urology Editorial Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Antagonists [adverse effects; *therapeutic use]; Naphthalenes [adverse effects; *therapeutic use]; Piperazines [adverse effects; *therapeutic use]; Prostatic Hyperplasia [*complications]; Prostatism [*drug therapy; etiology]; Randomized Controlled Trials as Topic; Sulfonamides [adverse effects; therapeutic use]

MeSH check words

Humans; Male